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Case Report

Screening for Pompe, Fabry, Gaucher Disorders Using Dried Blood Spot: 3 Years Experience

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Abstract

Lysosomal storage diseases (LSD) are a group of 50 metabolic diseases, with the origin changes cause by bad function of the lysosome.

The purpose of this study is find cases of Pompe, Fabry or Gaucher disorders, using dried blood spot (DBS) during a period of 3 years.

The screening of these 3 disorders was during a period of 3 years, in two hospitals, one public in Macau, China and another private in Portugal, between 1-1-2020 to 31-12-2020 and 1-1-2023 to 31-12-2024, respectively.

We used DBS samples for enzyme study.

The criteria for determination was based on the flowchart designed by the author for Pompe, Fabry and Gaucher diseases.

All positive test need to be confirmed by whole blood and DNA study.

A total of 27 cases (Macau: 16, Portugal: 11) were screened using flowchart criteria:

Pompe - 22, Fabry - 2, Gaucher - 3.

The age of the patients was between 1 month to 31 years old.

The gender ratio was 1:1

We confirmed 3 cases, one of each diseases.

Whenever we have a patient with clinical symptoms, the first step is to do the enzymatic screening in the filter paper. The confirmation test is DNA study.

We can offer prenatal diagnosis and genetic counselling for the future pregnancy in these 3 diseases.

Keywords: *Pompe; Fabry; Gaucher; Dry Blood Spot*

Introduction

Lysosomal storage diseases (LSD) are a group of 50 metabolic diseases, with the origin changes cause by bad function of the lysosome.

The majority of LSD are autosomal recessive disorders.

Only 3 are recessive x-linked: Fabry, Hunter and Danon.

Enzyme replace therapy (ERT) is the treatment of choice of some of diseases.

The diagnosis can be realized in filter paper with only some drops of blood.

LSD is classified in 3 main types (Table 1).

MUCOPOLISACARIDOSIS (MPS)	SPHINGOLIPIDOSIS	OLIGOSSACARIDOSIS	OTHER
MPS I H/S - Hurler / Scheie	Fabry	Alfa-Manosidosis	Cistinosis
MPS II - Hunter	Gaucher type I	B-Manosidosis	Multiple Sulfatidosis
MPS IIIA - Sanfilippo A	Gaucher type II/III neurologic form	Aspartilglucosaminuria	Pompe
MPS IIIB - Sanfilippo B	Krabbe	Schindler	Danon normal activity of acid maltase
MPS IIIC - Sanfilippo C	Niemann-Pick Tipo A/B	Fucosidosis	Salla
MPS IIID - Sanfilippo D	Niemann-Pick Tipo C	Galactosidosis	Mucolipidosis II or I cell
MPS IVA - Morquio A	Gangliosidosis GM1	Sialidosis	Mucolipidosis III A
MPS IVB - Morquio B	Gangliosidosis GM2		Mucolipidosis III C
MPS VI - Maroteaux-Lamy	Metacromatic Leucodistrophy		Mucolipidosis IV
MPS VII - Sly	Wolman		Lipofusinosis
MPS IX	Farber		NCL 1 to 8

Table 1: *Classification of LSD.*

Clinical symptoms

The clinical presentation of LSD is variable: coarse face, macroglossia, multiple dysostosis hepatosplenomegaly, cardiomyopathy and so on (Table 2).

• Coarse face	• Convulsive crisis	• Anemia
• Macroglossia	• Behaviours problems	• Cardiomyopathy
• Hirsutism	• Hearing problems	• Arrythmia
• Umbilical hernia	• Corneal opacity	• Angiokeratoma
• Multiple disostosys	• Cherry red spot	• Ictiosis
• Hepatomegaly	• Catarats	• Subcutaneous nodules
• Splenomegaly	• Optic atrophy	• Proteinuria
• Psycomotor regression	• Strabism	• Tubulopathy
• Ataxia	• Macular degeneration	• Hoarseness
• Acroparesthesias	• Ophtalmoplegia	• Articular rigidity

Table 2: *Clinical symptoms.*

In this article we are going to review 3 disorders of LSD, that we can treat with enzyme replace therapy (ERT).

Pompe disease

It´s caused by reduction of activity of alfa-glucosidase-acid.

Heart, respiratory and skeletal system are more affected.

In the severe form, death occurs in the first year of life secondary to heart and respiratory failure.

In the late presentation, muscle debility is progressive, and the child will need wheelchair and/or ventilator support.

It´s an autosomal recessive disorder. The incidence is 1/40.000 newborns.

World prevalence is around 5.000 to 10.000 cases.

There are mainly two types of presentation: infantile and late onset.

The infantile onset affected muscle-skeletal, lungs and heart, and the prognosis is bad, if we don't diagnose at the beginning (Table 3).

• Pompe: Infantile onset			
• Muscle -skeletal	• Lungs	• Heart	• Other symptoms
• Progressive muscle weakness	• Progressive respiratory insufficiency	• Cardiomegaly	• Difficulty in swalloing, eat and breastfeeding
Hypotonia	Frequent respiratory infections	Left ventricule hypertrophy	• Psycomotor development delay
• Motor delay			• Hepatomegaly
• Macroglossia			
• Absent of reflex			

Table 3: *Infantile onset.*

The late onset also affected same organs, but the prognosis is better. The muscle weakness is progressive, with exercise intolerance (Table 4).

• Pompe: Late onset		
• Muscle -skeletal	• Lungs	• Other symptoms
• Progressive muscle weakness	• Respiratory insufficiency	• Difficulty in swallowing and eat
• Unstable walking - tip of the feet	• Ortopnea	• Hepatomegaly
• Low back pain	• Sleep apnea	• Morning headache
• Reduced reflex	• Effort dyspnea	• Night sonolence
• Difficulties in climbing stairs	• Exercise intolerance	
• Scapula alata	• Respiratory infections	
• Gowers signs (distrophy as result of extreme muscle weakness)		
• Psycomotor development delay		
• Lordosis, scoliosis		

Table 4: *Late onset.*

In the figure 1, we can see some important symptoms of Pompe disease.

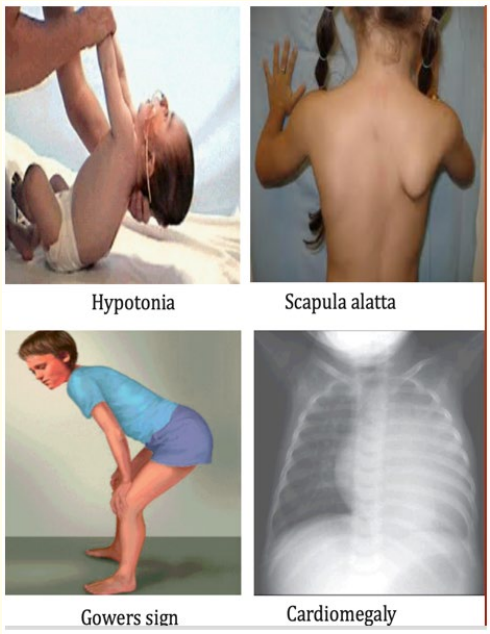

Figure 1: *Some symptoms of Pompe disease.*

Diagnosis

Enzymatic screening in filter paper, skin biopsy for study of fibroblast and determination of the activity of alfa-glucosidase-acid and gene test.

Creatine kinase (CK) is a very sensitive marker of Pompe disease, particularly in the infantile form (2.000 IU/L).

In adults CK can show normal parameters.

Treatment

Myozyme contain the active substance alglucosidase alfa "DNA recombinant technology".

It is given in IV perfusion of 20 mg/Kg 2/2 weeks.

The perfusion is given in the slow rhythm in the beginning and later we increase gradually.

Fabry disease

Fabry is a x-linked autosomal recessive disorder cause by incapacity to produce an enzyme call alfa-galactosidase or alfa-GAL.

Without this enzyme, globotriaosilceramide or GL-3, keep in the cells.

The result is the accumulation of this material in the blood vessels, affecting the brain, heart and kidneys.

The incidence is 1/40000 in male individuals.

Clinical symptoms

The symptoms starts between 6 and 9 years of age.

Pain is the first symptom and also the most common.

Appears when the temperature change, the patient is exposed to high temperatures, fever or excessive hot weather, stress and tiredness.

Most patients showed 2 types of pain: acroparesthesia and "Fabry crisis".

Acroparesthesia: The pain is in the hands and feet. It's like a burn that can affect the patient daily or not.

"Fabry crisis": Episodes of intensive pain, like burn, initially in the hands and later in the feet and later in other parts of the body. Can take minutes or weeks

There are some pathognomic signs of Fabry disease: angiokeratoma and cornea verticillate (Figure 2).

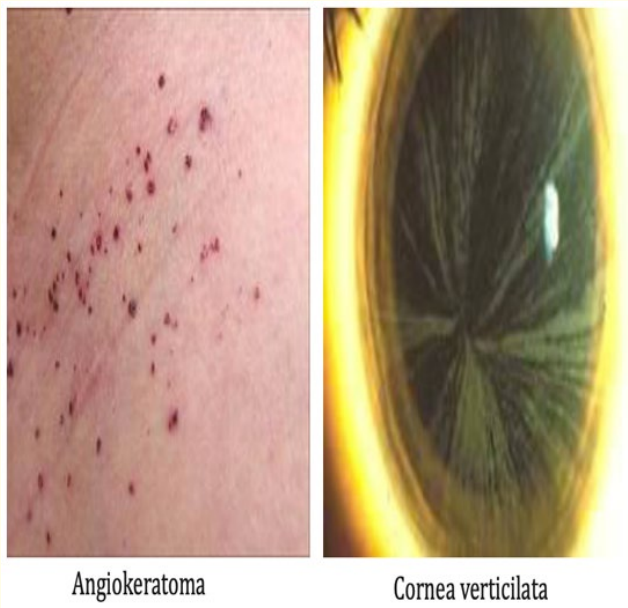

Figure 2: *Pathognomic features.*

Diagnosis

The diagnosis is confirmed by blood analysis with enzymatic examination of alfa-GAL activity and study of genetic mutation (DNA analysis).

Treatment

Fabrazyme is a solution for perfusion and contain the active substance - agalsidase beta.

The dose is 1 mg/Kg, every 2 weeks. The initial dose is better not to be more than 0,25 mg/min (15 mg/h), and can be increase in future perfusions.

This dose can be used in children from 8 to 16y.

Patients with severe renal disease can respond more slowly.

GL-3 level reduced in blood of the patients using Fabrazyme, with normal levels after 20 weeks of treatment.

The treatment improved their symptoms and quality of life.

Gaucher disease

It´s cause by enzymatic deficiency of glucocerebrosidase.

Glucocerebroside accumulate progressively in the macrophage and them increase the size and later will change to Gaucher cells with accumulation in the liver, spleen, bone marrow and can cause spontaneous bone fractures.

It´s an autosomal recessive disorder.

The incidence is 1/100000.

Clinical symptoms

The patient present with pale, asthenia, bleeding, particularly epistaxis because of low platelets levels, bruise and hematoma, legs and bone pain (spontaneous fracture) and pain and abdominal distention secondary to hepatosplenomegaly.

There are 3 types: type 1, the most frequent with neuropathic and non neuropathic forms. The patient can be asymptomatic. Type 2, the most severe form with hepatosplenomegaly and severe anemia and type 3; the symptoms starts in in the infancy and osteopenia can cause fractures (Table 5).

Type 1	Type 2	Type 3
• It´s the most frequent • There are two forms: non neuropathic or non neuropathic form of adult • The patients can be asymptomatic or showed hepatosplenomegaly, hematologyc changes or bone fractures	• Acute neuropathic or infantile neuropathic form • Hepatosplenomegaly, severe hematologic changes and dead in the first 2 years of life	• Sub-acute neuropathic or juvenile neuropathic form • Hepatosplenomegaly, anemia, thrombocytopenia, bone fracture or pain, slowly progressive neuropathy • The symptoms starts since infancy and dead occurs between 20 to 40 years of age.

Table 5: *Clinical symptoms.*

Hepatosplenomegaly, osteopenia and Gaucher cells are typical in Gaucher disease (Figure 3).

Figure 3: *Some important signs of Gaucher disease.*

In the Ashkenazi Jewish Origen, the frequency of Gaucher disease is very high - 1:800, with hematologic evolution to malignancy in 1: 2500.

Symptoms of gall stones, abdominal discomfort, splenic nodules, pregnancy associated with thrombocytopenia, post-partum hemorrhage, bone pain and gammopathies are important information to support a suspicious of Gaucher disease (Table 6).

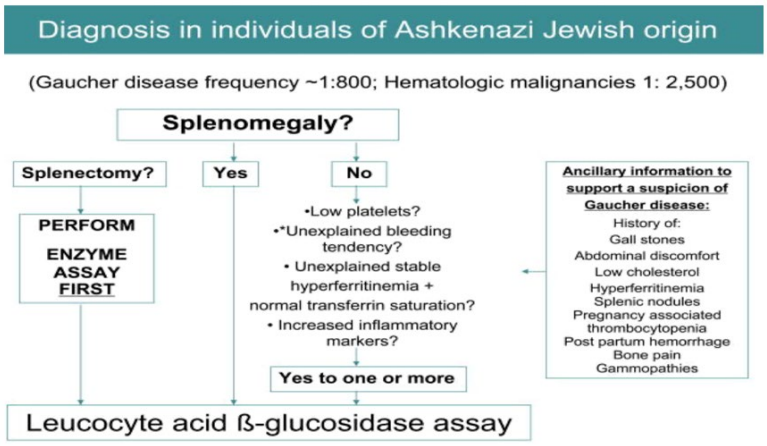

Table 6: *How we suspect of Gaucher disease.*

Treatment

Cerezyme (imiglucerase) use DNA recombinant technology and is indicated in type 1 and 3 with not significant neurological changes.

The dose is 60 U/kg 4-4 weeks.

The initial perfusion is 0,5 U/kg/min and later change to the maximum dose of 1,0 U/kg/min.

The hematological and visceral changes become better and stop the progression to bone disease.

Purpose

The purpose of this study is find cases of Pompe, Fabry or Gaucher disorders, using dried blood spot (DBS) during a period of 3 years.

Material

The screening of these 3 disorders was during a period of 3 years, in two hospitals, one public in Macau, China and another private in Portugal, between 1-1-2020 to 31-12-2020 and 1-1-2023 to 31-12-2024, respectively.

Methods

We used DBS samples for enzyme study of these 3 disorders.

The criteria for determination was based on the flowchart for Pompe, Fabry and Gaucher diseases.

The flowchart was designed by the author, based on references that are in the footnote of each chart (Figure 4-6).

All positive test need to be confirmed by whole blood and DNA study.

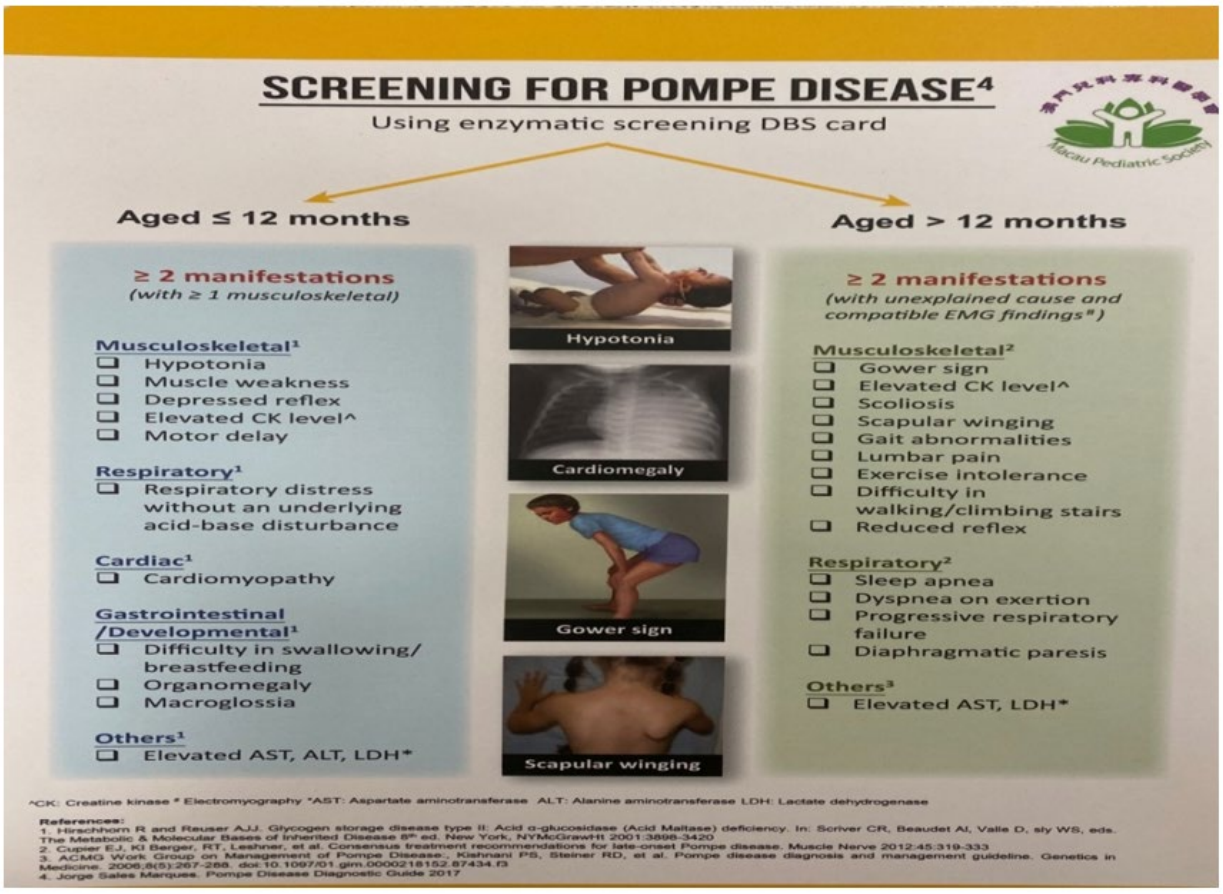

Figure 4: *Pompe flowchart.*

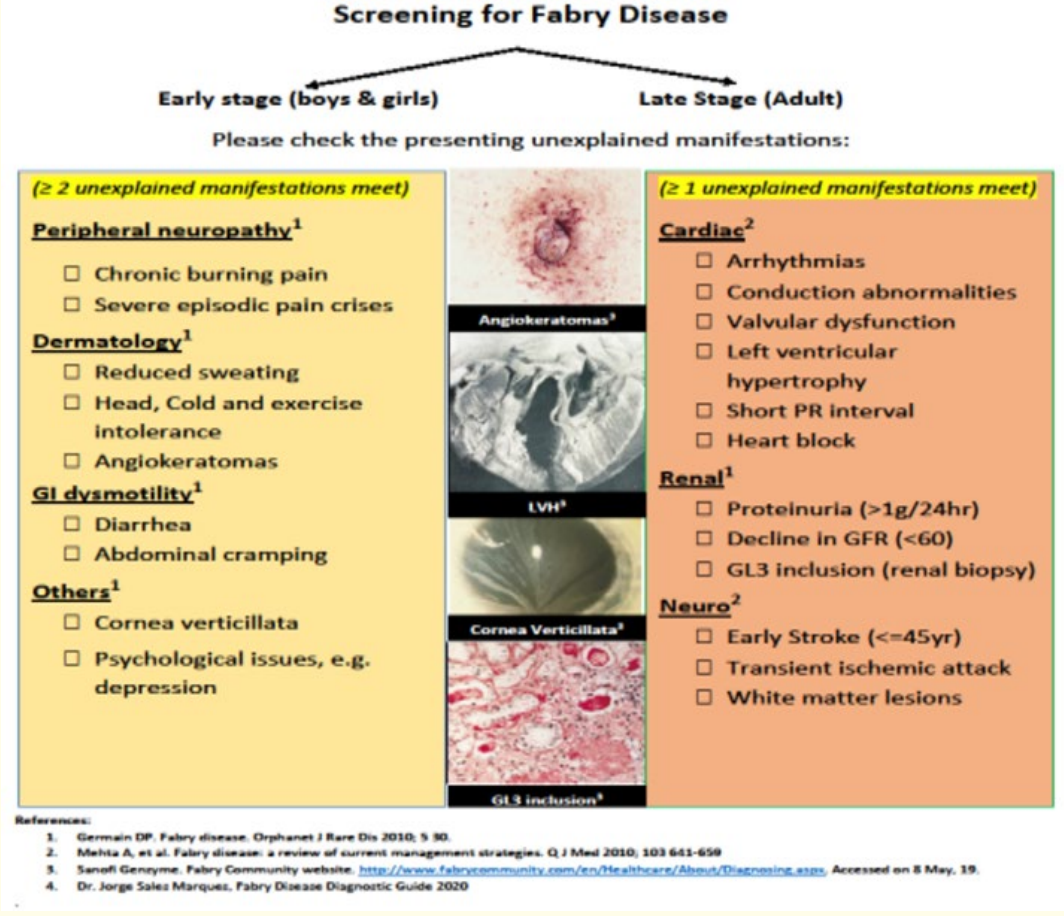

Figure 5: *Fabry flowchart.*

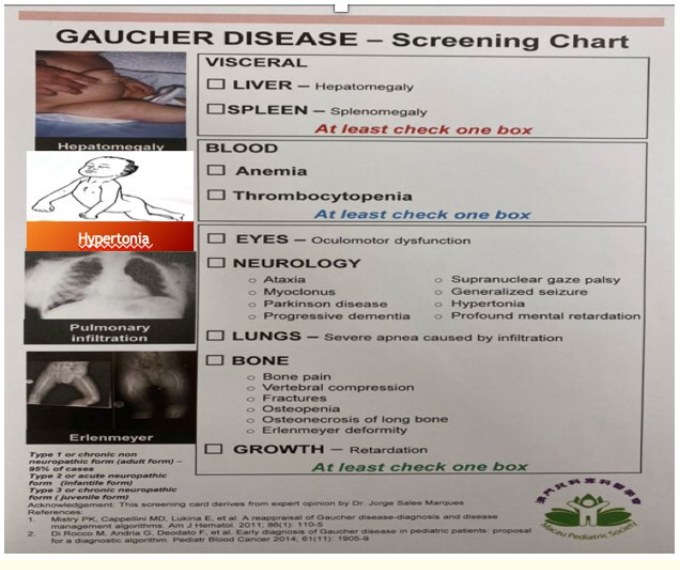

Figure 6: *Gaucher flowchart.*

Results

A total of 27 cases (Macau: 16, Portugal: 11) were screened using flowchart criteria:

- Pompe - 22
- Fabry - 2
- Gaucher – 3.

The age of the patients was between 1 month to 31 years old.

The gender ratio was 1:1.

We confirmed 3 cases, one of each diseases (Table 7).

	Pompe - 22	Fabry - 2	Gaucher - 3
Main symptoms for screen	▪ *Hypotonia* ▪ *Scoliosis* ▪ *Scapula alata* ▪ *Cardiomyopathy* ▪ *Weak muscle* ▪ *Ck high*	▪ *Angiokeratoma* ▪ *No sweating*	▪ *Spontaneous fractures* ▪ *Pancytopenia*
Cases confirmed	*1*	*1*	*1*

Table 7: *3 cases confirmed.*

Cases of Pompe, Fabry and Gaucher

Case 1: Pompe disease

2 years old boy, with:

* Muscle weakness.
* Difficulty in climbing stairs.
* 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).

Figure 7

Case 2: Fabry disease

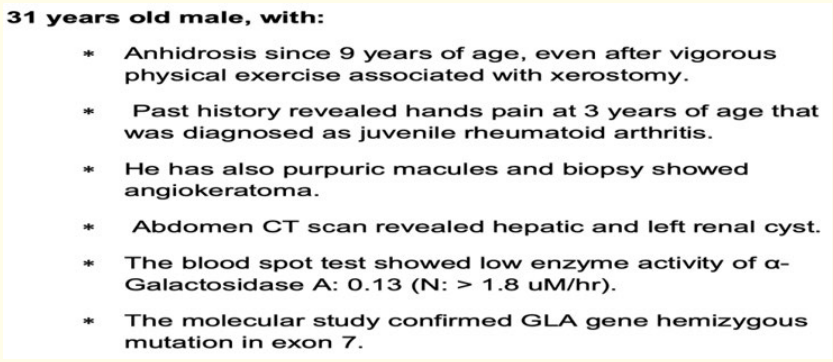

Figure 8

Case 3: Gaucher disease

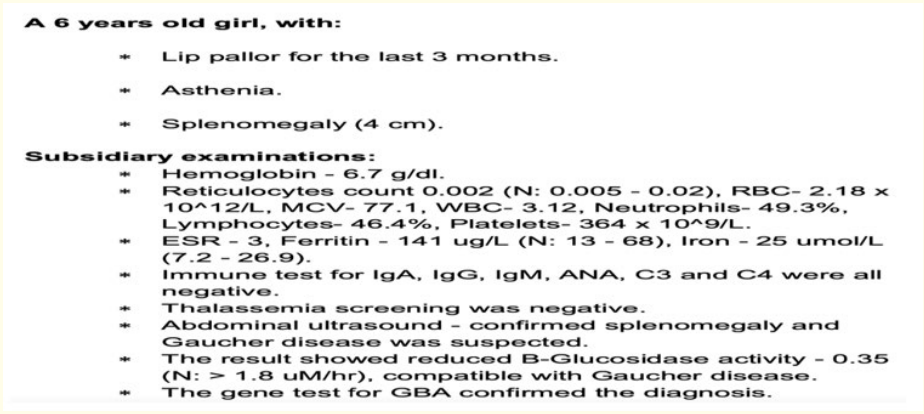

Figure 9

Discussion

Enzyme replace therapy in diseases like Pompe, Fabry, Gaucher has change the final prognosis of these patients, giving them a better quality of life and decreasing the risk of death.

These 3 disorders are underdiagnosed because they affected multiple organs and systems.

The patient can be lost in different consultations, like pediatrics, neurology, orthopedics, hematology, cardiology and physical medicine and rehabilitation.

Whenever we have a patient with clinical symptoms, the first step is to do the enzymatic screening in the filter paper.

The confirmation test is DNA study.

We can offer prenatal diagnosis and genetic counselling for the future pregnancy in these 3 diseases.

Pompe and Gaucher are inherited as autosomal recessive disorder and Fabry is a x-linked disease.

Conclusion

If we suspect of Pompe, Fabry or Gaucher disorders, we can do the DBS for screening.

The earlier we diagnose the disease, the better will be the prognosis and quality of life of the patient [1-11].

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