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Gaucher's disease in Rwandan patients, diagnostic and therapeutic challenges: a case series

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ABSTRACT

INTRODUCTION: Gaucher disease is a rare genetic disorder due to deficiency of glucocerebrosidase. Its symptoms are similar to the common hematological, tropical and neurological diseases challenging most of the clinicians.
Prompt treatment is crucial to prevent life-threatening complications but high cost of the enzyme replacement therapy (ERT) makes its management very challenging in resource-limited setting as reported in two cases below.

CASES

We report on two children who presented with a history of nose bleeding, abdominal distension, fever, and recurrent anemia needing repetitive transfusions. Both had hepatomegaly and very massive splenomegaly.
The first child was treated as a case of tropical splenomegaly for a year without improvement and later the inborn error of metabolism was suspected and Gaucher disease confirmed after being transferred to India for testing. A homozygous missense mutation c.1448T>C p.(Leu483Pro) was identified in GBA gene. According to HGMD Professional 2019.1, this variant has previously been described as disease causing for Gaucher disease type 1.
The ERT became available later under the support from Pfizer then the patient was treated and he improved his clinical condition.

The second patient presented at 2 years of age with symptoms while her twin was completely healthy. She was diagnosed to carry the same missense mutation c.1448T>C p.(Leu483Pro) causing Gaucher disease type 1. Unfortunately, she died as the pediatric team was still trying to get ERT. The remaining twin was also diagnosed with Gaucher disease type 1 and later on she started having episodes of anemia and thrombocytopenia. Her ERT was promised by SANOFI Genzyme and she was still waiting for treatment when we reported these observations.

CONCLUSION

Reporting these cases highlights the need for awareness and consideration of Gaucher disease among differential diagnoses made by clinicians. It also stresses the need for timely affordable and accessible diagnostic tools and treatment, as early diagnosis and treatment are crucial for good outcome..

Keywords: Gaucher disease; glucocerebrosidase; lysosomal storage; Enzyme Replacement Therapy; macrophage

INTRODUCTION

Gaucher disease (GD) is lysosomal glycosphingolipid storage disorder due to a deficiency of the lysosomal acid ß-glucocerebrosidase [1]. This causes accumulation of Gaucher cells (the sphingo- lipid glucosylceramide in lysosomes of macrophages) in the liver, spleen, bone, and bone marrow commonly [2][3] causing a very wide variety of clinical presentations. Signs and symptoms are very often similar to the other common hematologic and neurological conditions which makes it very challenging to clinicians leading to missed or delayed diagnosis [2].

We report on these cases to raise local awareness of health professionals upon the occurrence of this disease. This is in order to stimulate an index of suspicion when similar cases present and to highlight difficulties faced by patients especially in getting the prescribed treatment. These two cases show that right and early diagnosis and treatment are associated with good outcome while delay is associated with high morbidity and mortality.

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CASE PRESENTATIONS

Case 1: C. L is an 8-year old boy presented at 2 years of age with 1.5 years history of progressive abdominal distension, recurrent nasal bleeding for 1 year and loss of appetite, weakness and intermittent fever. He was treated with mefloquine and transfused several times with packed Red Blood Cells and platelets for the period of 1 year as a case of tropical splenomegaly without resolution of symptoms.

Physical examination revealed a stable child with pallor, cervical lymphadenopathy and right jugulodigastric lymph node-2cm, not tender, gross splenomegaly 14 cm below costal margin crossing midline with a smooth surface and hepatomegaly 8 below costal margin.

Full blood count showed hypochromic microcytic anemia with Hb, thrombocytopenia. Liver function test was normal, stool occult blood was negative and malaria antigen was negative too. Blood sickling test was negative and Activated Partial Thromboplastin Time (aPTT) was slightly increased.

Abdominal ultrasound confirmed hepatomegaly with increased echogenicity and massive splenomegaly.

At RMH, the pediatric team suspected inborn error of metabolism but unable to run tests for diagnosis at RMH, they decided to transfer the child to India where Essay for beta glucosidase enzyme showed the affected value suggestive of GD (Table1).

Table 1: Essay for beta glucosidase enzyme showing the affected range suggestive of GD

Essay of Beta-Glucosidase enzyme (Gaucher disease): Fluorometry method using artificial substrate				
Sample	Patient	Ref. Range	Mean	Patient range
Leukocytes	4.45	10-45 (nmol/hr/mg)	18.2	< 6
Dried Blood Spot		2.1- 18.43 (nmol/hr/ml)	5.01	< 1.16

The value of the control enzyme Beta-galactosidase (200.6 nmol/hr/ml) is in the normal range while the value of Beta glucosidase enzyme is in the affected range suggestive of Gaucher disease

A homozygous missense mutation c.1448T>C p.(Leu483Pro) was identified in GBA gene. According to HGMD Professional 2019.1, this variant has previously been described as disease causing for Gaucher disease type 1 He did not get ERT immediately due to the high cost and was transfused with 3 units of whole blood and 4 units of platelets. He then underwent splenectomy successfully to relieve symptoms while waiting for being supported to get ERT. After splenectomy he improved and was discharged from the hospital in stable condition on Azithral Syrup 100mg twice a day, Tranexa tab 250 mg twice a day, Monocef IV 1mg once a day and he came back to Rwanda.

Later his parents managed to get IV Elelyso supported by military medical insurance and Pfizer. Elelyso is given each 2 weeks and it has led to the improvement and child's normal life and even good school performance. No more anemia, no more bleeding, hepatomegaly progressively reduced in size, no more fever and the child gained energy and appetite from the time he started Elelyso as reported by his mother. Laboratory control tests showed improvement (Figure 2).

Table 2: Blood count test after getting ERT showing normal platelets and hemoglobin

	Result	Unit	Minimum	Maximum
Hemoglobin	13.8	g/dl	12	18
Hematocrit	45.8	%	34	50
Mean Corpuscular Volume	81.1	Fl	71	100
Platelets	400	10^3/ uL	150	450

His follow-up continued in RMH where he is regularly injected with taliglucerase alfa (Elelyso) and undergoes regular check-ups.

Case 2: I. A. was a 2-year-old girl who presented with a 1-year history of progressive abdominal distension associated with recurrent episodes of fever, respiratory distress and anemia refractory to transfusions. The parents also reported weight loss, night sweat, cough, vomiting and epistaxis despite frequent hospital admissions and various treatments and inability to hit major growth milestones.

She was the second child of the family born from term twin-pregnancy and her twin was healthy.

Physical examination revealed a lethargic, cachectic, tachypneic, tachycardic and irritable child with SPO_2 of 78% on room air and armpit temperature of 37.9°C. She had palmoplantar paleness. She had nasal flaring, intercostal muscle retraction and used accessory respiratory muscles. She also had distended abdomen with splenomegaly stage IV and hepatomegaly at 5 cm below the costal margin.

Malaria, leukemia, pneumonia, hemolytic diseases were the differential diagnoses at the beginning and laboratory tests showed a negative malaria blood smear. She had leukocytosis, severe thrombocytopenia, severe anemia (Hb=4.7g/dl), normal

MCV, raised CRP, hypoalbuminemia as well as very raised liver transaminases.

Peripheral blood film showed only normocytic normochromic anemia with persistent thrombocytopenia.

She was transfused with platelets and packed red blood cells. Blood count control tests consistently showed thrombocytopenia and low hemoglobin a day after transfusion. She kept having multiple episodes of epistaxis and depending on multiple transfusions (platelets and packed red blood cells) after each 2-3 days. The leukocytosis and fever subsided too on amikacin and ciprofloxacin for the first 3 days of medications and later fever returned and she kept needing oxygen therapy.

GD was suspected and RMH pediatric team collaborated with CENTOGENE Biotechnology Company to run genetic tests for both the patient and her twin.

They did lyso Gb1 concentration analysis and GBA sequencing which confirmed it for both twin patients.
The same missense mutation c.1448T>C p.(Leu483Pro) causing Gaucher disease type 1 like in the first patient was detected in both patients.

With the support of charitable SANOFI Genzyme, Enzyme Replacement Therapy was ordered from abroad as it was not available in Rwanda. While waiting for ERT, splenectomy was planned after becoming stable with improvement in platelet counts. She, unfortunately, kept worsening instead and a week later she deteriorated and died of spontaneous bleeding before the arrival of the therapy.

DISCUSSION

GD is an autosomal recessive genetic disorder with equal sex distribution [4] and onset ranges widely from 3 months to 80 years of age because some patients develop complications at a very early age while others remain asymptomatic for almost entire life and sometimes they are investigated after an incidental finding of organomegaly [2][5]. This may be the reason why in our report, the second child had symptoms while her twin remained completely healthy.

Its prevalence is higher in Ashkenaz Jews at 1 in 850 individuals while worldwide it is 1 in 50,000 to 100,000 [4]. It was evidenced that the biochemical abnormality found in GD in Kenyan, Ugandan, the Congolese and Nigerian children, and in African-Americans is not as rare in the negroid race as has been thought and may be widespread on the African continent [6].

GD is divided into 3 clinical types, of which type 1 is by far the most common. In type 1, which is the most common, Gaucher cells accumulate in the liver, spleen, bone marrow, skeleton and the lung while in type 2 and 3, in addition to those organs, the brain is affected (hence the name neuropathic GD) [2][7]. The onset of clinical features may occur at any age in type 1, in infancy in type 2 and in early childhood in type 3 [1].

As seen in these reported cases, patients commonly presented hepatomegaly with very massive splenomegaly especially in Type 1 GD and the resulting hypersplenism. Minor liver enzyme elevation occurs but the presence of jaundice or poor liver functions indicate poor prognosis [1].

Gaucher cells in the skeleton causes bone infarction and pain crises, pathologic fractures and osteosclerosis avascular necrosis similar to sickle cell bone manifestations [8].

Hematologically, GD presents with anemia and thrombocytopenia and both our reported patients had such hematological manifestations. These leads to fatigue, growth delay, bruising and bleeding [8] [9] as reported in our cases as episodes of epistaxis. Skin manifestations are diffuse pigmentation, easy tanning and flitting brown macules [10].

Type 2 GD is rare and is characterized by a rapid neurodegenerative course. Patients with type 2 GD may present with hypertonicity, seizures, strabismus, dysphagia, failure to thrive, and oculomotor apraxia and laryngospasm. These commonly lead to death within 2 years from brain stem involvement that compromise respiration [4].

In addition to organomegaly and bony involvement, type 3 GD patients have gaze palsies, myoclonic epilepsy, nerve deafness and learning disabilities, or develop dementia [3].

Testing glucocerebrosidase activity in peripheral blood leukocytes confirms the diagnosis by finding less than 15% of mean normal activity. Histological tests are key for detecting the presence of Gaucher cells in the macrophage-monocyte system in the bone marrow or in liver biopsy samples [3]. This is discouraged because blood enzyme test is sensitive and specific and less invasive [1].
Molecular test in Ashkenazi patients detects GBA mutations while in other ethnicities, sequencing of the exons of GBA is necessary [4]. This was done in our second case while glucocerebrosidase activity test was done in the first case. Thus these 2 are major tests to confirm GD.

The identified missense mutation c.1448T>C p.(Leu483Pro) has been classified as pathogenic (class 1) according to the recommendations of Centogene and ACMG. This mutation is a common mutant allele encountered in many different populations [12-16]. The high frequency and worldwide distribution of the leu444pro mutation indicates that the site may be a 'mutational hotspot' for a T-C nucleotide transversion on c.1448 of GBA [17].

Full blood count and peripheral blood film, iron, folate and Vit B_{12} should be asked to rule out other anemia causes. Renal and liver profiles, CRP and endocrine profile, as well as clotting tests and viral screens (HIV, hepatitis) can be performed as indicated [1].

Skeletal and chest X-ray help diagnose bone involvement, fractures and pulmonary involvement or cardiomyopathy, respectively. Ultrasound detects visceromegaly, liver, renal infiltrations and bone involvement too [1].

Enzyme replacement therapy (ERT) is the gold standard treatment for GD [1] and early initiation of treatment decreases irreversible complications of GD. The ERT improves growth, weight gain and energy levels. Imiglucerase (Cerezyme), velaglucerase alfa (VPRIV), and taliglucerase alfa (Elelyso) replaced symptomatic therapies such as transfusion, analgesics and splenectomy [4]. Visceral and hematological responses such as up to 52% decrease in spleen and liver volumes and the improvement in hemoglobin concentration and a rise in platelet counts have been observed [3]. However, no reverse of osteonecrosis, osteofibrosis, and lytic lesions and pulmonary involvement was seen.

Aminosugar inhibitor of glucosylceramide synthase, which is an oral substrate reduction therapy, is the alternative for patients allergic to the gold standard ERT.

Our first patient had to undergo splenectomy as a symptomatic treatment while waiting for the availability of the ERT. The second patient was diagnosed but she did not receive ERT because she had bleeding and later died before the ERT gets available. It had to be imported from abroad with financial support from SANOFI Genzyme but the process to get support to import it took longer for the child to survive.

These challenges were also reported in Morocco where all 11 cases reported so far received only symptomatic treatment such as analgesia, transfusions and splenectomy [4].

It was estimated that the average yearly ERT medication costs are €124,000 to €258,000 per patient (124 to 258 millions Rwandan francs) and the lifetime costs of ERT are roughly €5,716,473 (Over 5.7 billions Rwandan francs) [11]. This makes ERT unaffordable to a patient in resource-limited countries. Fortunately, some health insurances accept to support patients with strong arguments.

Patient with type 2 GD tend to have persistent or progressively fatal brain involvement even on treatment. Symptomatic patients with type 1 or type 3 GD who receive treatment have a very good prognosis. Under treatment, hemoglobin and platelet count raise and organomegaly reduces [4] and this also was the case for our patient who managed to receive the therapy. It is estimated that life expectancy in patients with type 1 GD may reach 68 years too [4].

In conclusion, it is important to include GD among differential diagnoses when patient presents with hematological, neurological and tropical diseases symptoms. The wide variety of its prevalence and symptoms should be considered. Clinicians should have a very high index of suspicion of GD to be able to diagnose it as early treatment is very crucial. Genetic testing is important to confirm the diagnosis. Measures to make ERT more affordable and easily accessible are important as it is proven that patients who receive treatment live a normal life.

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