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The Iraqi Experience in the Treatment of Gaucher Disease in Children by Enzyme Replacement therapy

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Abstract:
Background: *Gaucher disease (GD) is the most common pan-ethnic inherited lysosomal storage disorder;it is subdivided into three typesandthe non-neuronopathic (type 1) is the most common type (93 %) in the western world. Gaucher disease (GD) produces a multisystem involvementand the most effective form of therapy inreversing the hematological and visceral manifestationsisenzyme replacement therapy (ERT) with recombinantenzyme imiglucerase.*
Objective: *The aim of the study is to determine the outcome of enzyme replacement therapy in children with gaucher disease for 6 monthsin Children welfare teaching hospital Baghdad- Iraq.*
Methods: *A descriptive retrospective study carried out in Children welfare teaching hospital, from the first of May 2013 to the first of December 2013 on 20patients, their age ranged from 20 months to 21years.*
Results: *Of the 20 patients, 15(75%) were males and 5(25%) were females. The commonest age of presentation for the disease was between 2-5 years in 11 patients (55%).*
It was found that easy fatigability affect all the patients (100%) ,splenomegaly in 80%, hepatomegaly in 75%, abdominal pain & ecchymosis/epistaxis in 70% for each.
The platelets count ranged from severe Thrombocytopenia to normal platelets counts with a mean of $(109\times10^{9)}$/L. But it was improved to a mean of 193×10^{9} /L after six months of treatment. The hemoglobin level ranged from severe anemia to almost normal hemoglobin value with a mean of 7.9g/dl, but it was raised to a mean of 9.8 g/dl.
It was found that clinical improvement was achieved by the hepatic regression which occurs in 75% of patient, and splenic regression occurs in 85%. The improvement in easy tiredness noticed in 90% of patients, and it was found interestingly that bleeding tendency improved in 100% of the patients.
Conclusions: *There must be a high index of suspicion about gaucher disease when a child presents with hepatosplenomegaly and/or cytopenia and/or bone pain. The diagnose of the disease with noninvasive techniques at early stages in view of the availability of an effective enzyme replacement therapy which leads toimprovement in bleeding tendencyand requirement for blood transfusion.*
Key Words: *Gaucher disease, enzyme replacement, children.*

I. Introduction

Gaucher disease (GD) is the most common pan-ethnic inherited lysosomal storage disorder (LSD), affectingapproximately 1:40,000 to 1:60,000 individuals globally [1, 2, 3, 4]. In Ashkenazi Jews, it is one of the most common genetic disorders, with a carrier frequency of 1:17 [5].This disease is due to inborn defects of the membrane-bound lysosomal enzyme, acid b-glucosidase, which is encoded by a gene located on chromosome, 1 q21-q31, and this will leads to an accumulation of glucocerebrosidase in the lysosomes of cells derivedfrom the monocyte/macrophage lineage in the reticuloendothelial system.[6]It is subdivided into three types: non-neuronopathic (type 1), acute neuronopathic (type 2), and chronic neuronopathic(type 3). The non-neuronopathic is the most common type (93 %) in the Western world and is distinguished from the other types by the lack of primary central nervous system involvement. [7]This multisystemic disease is characterized by hematologic problems, organomegaly, and skeletal involvement; the latter usually manifested as bone pain and may end with pathologic fractures. [8] About 300 mutations have been identified in GD patients, including deletions, insertions, frame-shift mutations, point mutations, splice site mutations and recombinants. The variety of phenotypes associated to GD shows imperfect correlation with mutations. [9]Gaucher disease (GD) produces a multisystem involvement characterized by progressive visceral enlargement and gradual replacement of bone marrow with lipid-laden macrophages. In children, visceral andhematologic manifestations tend to appear earlier than bone manifestations. As in adults, visceral findings are almost universal in patients at diagnosis—95 % of children have splenomegaly and 87 % have hepatomegaly at time of diagnosis. [10, 11]Symptomatic anemia, hepatosplenomegaly, coagulation abnormalities and structural skeletal changes occur at some point during the course of illness in most patients.Skeletal involvement is a major cause of morbidity, afflicting up to

75% of patients, but varies widely between and within individual patients. [10]The most effective form of therapy inreversing the hematological and visceral manifestations ofGaucher's disease(Type 1)isenzyme replacement therapy (ERT) with recombinantenzyme imiglucerase.[10]However many patients underwent surgical treatment in the form of splenectomy to correct their pancytopenia but it should be prevented since it leads to an increased tendency to infections and a worsening of bone disease [13].

II. Aim Of The Study

The aim of the study is to determine the outcome of enzyme replacement therapy in children with Gaucher disease for 6 month in Children welfare teaching hospital Baghdad- Iraq.

III. Patients And Methods

A descriptive cross-sectional retrospective studyconducted on twenty patientsand the age of the study group was between (20 months-21 years). They wereadmitted to the Gastroenterology and Hepatology unit in Children Welfare Teaching Hospital/ medical city complex / Baghdad,during the period from the first of May 2013- first December 2013.Thepatients were referred to our center from all over Iraqi hospitals and were diagnosed in our tertiary hospital.

The diagnosis of GD was based on:-

- clinical assessment: -detailed history with special concentration on family history of similar conditions or death and consanguinity and thorough clinical examination with focusing on growthparameters, hepatosplenomegaly with abdominal distension and its pressure symptoms, pallor, bleeding manifestation and full cardiac and neurological examination.
- Laboratory investigations:- included complete blood count (CBC), blood film and reticulocyte count (anemia, leukopenia and thrombocytopenia (were defined according to the age and sex specific values), prothrombin time (PT) and partial thromboplastin time (PTT), liver function tests, renal function tests, bone marrow aspirate (done only in fit patients). But liver biopsy could not be done because of the critical situation of all patients in the study group.
- Radiological investigations included plain X-ray for long bones and chest, abdominal ultrasonography to evaluate liver and spleen volumes, echocardiography, and MRI of femurs for selected patients.
- The precise diagnosisrelayson bone marrow examination that was done in7 patients which showed typical gaucher cellsand also confirmed in addition to the remaining 13 patients, by direct determination of (acid b-glucosidase) activity in peripheral blood leucocytes through metabolic laboratory /Hamburg university medical center.

IV. Results

Of the 20 patients included in this series 15(75%) were males and 5(25%) were females as shown in table -1.The commonest age of presentation for the disease was found between 2-5 years in 11 patients, it accounts (55%) as shown in table -2.

Regarding the clinical presentations, it was found that easy tiredness affect all the patients (100%) ,splenomegaly in 80%, hepatomegaly in 75%, abdominal pain& ecchymosis/epistaxis in 70% for each.

While the skeletal manifestations presented as bone pain & short statures in 55%, multiple fractures in 10%, but no cases of scoliosis. As shown in table-3.

The hematological situations of the patients before initiation of the treatment and regarding platelets count ranged from severe thrombocytopenia (13×10^9)/Lto normal platelets counts (390×10^9)/L with a mean of ($109\times10^{9)}$/L,but it was improved to a mean of 193×10^9/L ranging from (57- 420×10^9)/L,after six months of treatment. And the hemoglobin level ranged from severe anemia (4.6g/dl) to almost normal hemoglobin value11.8g/dl with a mean of 7.9g/dl,but it was raised to a mean of 9.8 g/dlranging from (6.7-13.4) g/dlas shown in table-4.

Regarding the clinical improvement it was found that hepatic regression occurs in 75% of patient, while splenic regression occur in 85%. The improvement in easy tiredness noticed in 90% of patients, and it was found interestingly that bleeding tendency manifested by Epistaxis/ Ecchymosis improved in 100% of the patients' .As shown intable-5.

Table- 1:- Sex distribution and consanguinity of the study sample

			Number	**Percentage**
Gender	Male		15	75%
	Female		5	25%
Consanguinity	Positive	First cousin's marriage	6	30%
		Second cousins' marriage	5	25%
		Far relatives	2	10%
	Negative		7	35%

Table- 2:- Patients age distribution of children with gaucher disease

Age group(years)	Number	Percentage
1 year - 2 years	4	20%
>2years- 5 years	11	55%
>5years- 10 years	3	15%
>10years- 15 years	1	5%
>15years- 20 years	0	0%
>20years	1	5%
Total	20	100%

Table- 3:- Clinical presentation at time of initiation of the treatment

Clinical presentations		Number		Percentage
		Positive	Negative	
Abdominal pain		14	6	70%
Splenomegaly		16	3	80%
			1splenectomized	
Hepatomegaly		15	5	75%
Epistaxis/ Ecchymosis		14	6	70%
Easy tiredness		20	0	100%
Skeletal manifestations	Bone pain	11	9	55%
	Short stature	11	9	55%
	Scoliosis	0	20	zero%
	Multiple fractures	2	18	10%

Table- 4:- Hematological situations beforeand after six months of initiation of the treatment

Indices	Level (range)	Level (range)
	Before treatment	After 6 month of treatment
Platelets (10^2/L) mean (range)	109×10^9 (13- 390×10^9)/L.	193×10^9 (57- 420×10^9)/L
Hemoglobin (g/dl) mean (range)	7.9 (4.6-11.8)g/dl	9.8 (6.7-13.4) g/dl

Table-5:- Clinical courses of patients with Gaucher disease after six monthsof the treatment

Clinical indices	Number	Percentage
Hepatic regression	15	75%
Splenic regression	17	85%
Easy tiredness improvement	18	90%
Epistaxis/ Ecchymosis improvement	20	100%

V. Discussion

Enzyme replacement therapy (ERT) has been proven all over the worldto be clinically effective for GD andcurrently is a standard treatment for type I and typeiii disease.Despite that ERT was available in many countries since 1991,but it did not reachour country only after 2012.Gaucher disease in Iraq is thought to be extremely underestimatedin part due toa lack of awarenesswith low index of suspicionaswell as lack of access to diagnostic tools.Out of 20 patients 15 of them are males (75%) and 5are females (25%) with male to female ratio 3:1and this percentage nearly similar to study done bykhalifa AS (6) in Egypt who revealed 3.5:1,Shehi B. Inalbania (14) which showed male to female ratio 1.75:1. But disagree with a results obtained byjy Lee (15) in Korea their ratio was0.82:1.It was found that consanguineous marriage present in 65% of cases while it was 88.8% bykhalifa A S(6) in Egyptand 50% in india by Nagral A et al(16) but there were no much focusing on this point in other countries which may explained by decreased prevalence of the inbreeding in other societies.

The first five years of life was the most common age group affected in this study (75% of the cases) which is closely related to result foundby Khalifa A S in Egypt(6),71% in japan by eto (17), and in India bynagral A et al(16), while the majority of type 1GD patients (66%) werediagnosed in adulthood (> 18 years old) in Iberia (Spain& Portugal) bygiraldo P.(18)

Regarding the clinical finding; the abdominal pain was present in this study in 70% of cases while it is 81.8% in Albanian children byshehi B et al (14)and it is common presentation mostly due to big spleen with its discomforting symptoms.

Splenomegaly was found in 80% of cases (one case was splenectomized 5%) and it is 90.9% by JY Lee et al in Korea (15) and 100% in Albania byshehi B et al (19), while in Romaniaby Drugan C et al (19) there was 40% with splenomegaly and 45% were splenectomized.

It was found thathepatomegaly present in 75% of patients while it is 85% in Romania bydrugan C et al(19) and 100% in Albaniaby Shehi B et al (14) and it is 68% in Iberia (Spain& Portugal) by Giraldo P.(18)

The bleeding tendency(manifested by ecchymosis& epistaxis) was present in 70% of cases while it is 27.27% in Shehi B. In Albania (14)and this can be explained by delays in the diagnosis of the disease until it reach advanced stage.

The skeletal manifestations ranged from 10% for pathological fractures to 55% for bone pain and short statures, whilein France45% of patients had skeletal symptoms (bone pain and / or bone crisis)by Rossia L.et al (20) and Korea by JY Lee et al (15), and in Romania the chronic bonepain (65%), pathologic fractures /hip replacement (20%) by Drugan C. Et al (19)in Romania.

The hematological manifestations revealed that dramatic improvement of platelets number and hemoglobin levelwere obtained after 6months of treatment and this result corresponds to othercasuistics in other countries (14, 15, 16).

It was found that we achieved dramatic regression of hepatosplenomegaly which is similar to study done in other countries (14, 16,21)

VI. Conclusions

There must be a high index of suspicion when a patient presents with hepatosplenomegaly and/or cytopenia and/or bone pain. The efforts should be focus at providing diagnose of the disease with noninvasive techniques at early stages in view of the availability of an effective enzyme replacement therapy which leads to dramatic improvement in the platelets count and hemoglobin level in addition to obvious regression in the hepatosplenomegaly.

Disclosures

Conflict of interest: none declared.

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