

# بسم الله الرحمن الرحيم





# شبكة المعلومات الجامعية التوثيق الالكتروني والميكرو فيلم





# جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

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# **Iron Homeostasis and Tissue Inflammation in Gaucher Patients on Enzyme Replacement Therapy**

*A Thesis*

*Submitted for Partial Fulfillment of Master Degree in Pediatrics*

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا  
إلا ما علمتنا إنك أنت  
العليم العظيم

صدق الله العظيم

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# *List of Abbreviations*

Abb.	Full term
ACD .....	Anemia of chronic disease
ACE .....	Angiotensin converting enzyme
AI .....	Anemia of inflammation
AID .....	Absolute iron deficiency
AVN .....	Avascular bone necrosis
BMI.....	Body mass index
BMT.....	Bone marrow transplantation
CBC .....	Complete blood count
CCL18.....	CC chemokine ligand 18
ChT .....	Chitotriosidase
CNS .....	Central nervous system
DMT1.....	Divalent metal transporter
ELISA.....	Enzyme-Linked Immunosorbent Assay
ERT.....	Enzyme replacement therapy
FID.....	Functional iron deficiency
FOV .....	Field of view
GCase .....	Glucocerebrosidase
GD.....	Gaucher disease
HGB.....	Hemoglobin
ICGG.....	International Collaborative Gaucher Group
IQR .....	Interquartile range
IRMA .....	Immunoradiometric assay
kg .....	Kilogram
LSDs .....	Lysosomal storage diseases
Lyso_GL1 .....	Glucosylsphingosine



## *List of Abbreviations Cont...*

Abb.	Full term
PARC .....	Pulmonary and activation-regulated chemokine
PAUS .....	Pelvi abdominal ultrasound
PCT.....	Pharmacological chaperone therapy
PLT .....	Platelet
S.....	Serum
SDS.....	Standard deviation score
SRT .....	Substrate reduction therapy
TFE.....	Turbo field echo
TIBC .....	Total iron binding capacity
TRAP .....	Tartrate-resistant acid phosphatase
TSAT.....	Transferrin saturation
WBC .....	White blood cells
WHO .....	World Health Organization
ZSSI .....	Zimran severity score index

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# INTRODUCTION

**G**aucher disease (GD), the most common of the lysosomal storage diseases (LSDs) (15%), was first described by Philippe Gaucher in 1882. It is a rare, autosomal recessive genetic disease caused by mutation in the GBA1 gene, located on chromosome 1 (1q21), leading to a decrease in the activity of a lysosomal enzyme, glucocerebrosidase (GCase) or by deficiency in the activator of GCase (saposin C) (*Roshan et al., 2017*).

Its incidence is around 1/40,000 to 1/50,000 births in the general population, but can reach 1/800 births in the Ashkenazi Jewish population (*Stirnemann et al., 2017*), it is classically categorized into three phenotypic variants, based on the presence (types 2 and 3) or absence (type 1) of central nervous system involvement (*Potnis et al., 2019*).

Type 1 GD (95% of cases) usually manifests with splenomegaly, hepatomegaly, anemia, thrombocytopenia, bone disease and delayed growth. Type 2 is characterized by a precocious and fast brainstem degeneration; these patients do not respond to treatment and death mostly occurs within the first two years of life. Type 3 GD patients have a slow evolving neurologic disease and usually present with seizures, eye movement abnormalities and mild systemic involvement with mean survival being to the third decade of life (*Alaei et al., 2019*).

Historically, GD1 was treated with supportive measures such as splenectomy and orthopedic procedures. Today, new therapeutics have dramatically altered the natural history of the disease both in children and adults. Approved therapies include enzyme replacement therapy (ERT) and substrate reduction therapy (SRT), other therapeutic strategies are currently in development (*Gary et al., 1018*).

ERT was developed, becoming the standard of care since 1991. It is based on the provision of sufficient exogenous enzyme to overcome the block in the catabolic pathway and effect the clearance of the stored substrate, glucosylceramide. Three of them are available: Imiglucerase, Velaglucerase alfa and Taliglucerase alfa. SRT is an alternative oral approach, based on reduced synthesis of glucosylceramide by inhibiting the appropriate synthetic resulting in decreased production of this dangerous lipid and the ability of the residual enzyme activity to reestablish a new steady state (*Linari & Castaman, 2016*).

Increased serum ferritin appears in more than 60% of people with GD at diagnosis. In GD there is an increased amount of iron in Gaucher cells, with no evidence of increased avidity between iron and GCase storage material. The excess of iron induces a conversion of hydrogen peroxide free radical that is very toxic to tissues through oxidation of proteins, peroxidation of membrane lipids and modification of nucleic acids (*Medrano-Engay et al., 2014*).