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بسم اللّه الرحمن الرحيم

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

شبكة المعلومات الجامعية

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قسم

نقسم باللّه العظيم أن المادة التي تم توثيقها وتسجيلها علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

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تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

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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✍ *Mohamed Nageh Abd Elhamed*

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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

Gaucher 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 al 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 restablish 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).***