INTRODUCTION

Gaucher disease (GD) is an inborn error of metabolism due to a deficiency of the enzyme glucocerebrosidase.

The disease is characterized by the engorgement of macrophage (Gaucher cells) by the substrate, glucocerebroside, leading to abnormalities of the spleen, liver, bones, lungs and brain

Three clinical types are recognized:

Type I: Non neuropathic GD I: In which there are only systemic manifestations of the disease.

Type II: Acute neuropathic GD II: With infantile onset and relentless neurological degeneration leading to death usually by age of 2 years.

Type III: Subacute neuropathic GD III: In which neurological involvement has a latter onset and a more variable course than GD II

(Beutler and Grabowski, 2001)

All three subtypes are inherited as autosomal recessive traits.

Type 1 disease has a striking predilection for individuals of Ashkenazi Jewish descent.

However type 3 was found to be the commonest type in Egypt ***(Khalifa et al., 1999).***

Classically, the pathophysiology of the Gaucher disease has been attributed to the amount, location, and rate of accumulation of the stored material. However, histology and pathology do not reveal massive glucocerebroside accumulation in the affected organs and tissues: e.g in the liver, glucocerebroside does not accumulate in the hepatocytes but only in the kupffer cells, and in the lungs, severe pulmonary involvement is not necessarily accompanied by alveolar Gaucher cells infiltration.

It has therefore been speculated that other factors, including environmental or acquired conditions, such as viral infection or pregnancy, each of which may trigger or aggravate symptoms and signs.

Oculomotor signs are universal in NGD. Their detection in GD is diagnostic of neuropathic disease, and in GD III, they may precede the emergence of overt neurological signs by many years ***(Harries et al., 1999).***

The main sign is severe difficulty (in GDIII) ***o***r virtually a total inability (in GDII) in generating saccades (oculomotor appraxia), when saccades can be made, they are usually slow, implicating brainstem saccades centers ***(Harris et al., 1999).***

Auditory brainstem responses (ABRs) have also been reported as abnormal in NGD although they have not been thoroughly investigated.

Abnormal ABRs may indicate involvement of central brainstem and/or peripheral auditory pathways. More refined localization of ABRs is uncertain and may even be confounded by peripheral hearing loss, which has not been discounted in NGD.

Additional audiological tests would provide a more powerful approach to understanding audiological pathway affected by NGD ***(Bamiou et al., 2001).***

For type 1 and most type 3 patients, enzyme replacement treatment with intravenous recombinant glucocerebrosidase (imiglucerase) can dramatically decrease liver and spleen size, reduce skeletal abnormalities, and reverse other manifestations.

Velaglucerase alfa has recently been introduced as an alternative to glucocerebrocidase. It is currently being tested in clinical trials.

Successful bone marrow transplantation cures the non-neurological manifestations of the disease, because it introduces a monocyte population with active beta-glucosidase ***(Grabowski, 2008).***

AIM OF THE WORK

The aim of the present study:

Is to assess neurologic symptoms and signs in a cohort of Egyptian patients with Gaucher disease by:

- Clinical neurologic examination.
- Evoked potentials:
    - Visual evoked potential
    - Auditory brainstem evoked potential
    - Somatosensory evoked potential.

LYSOSOMAL STORAGE DISEASE

The lysosomal storage diseases are group of genetic disorders that result from defects in lysosomal functions.

What are lysosomes?

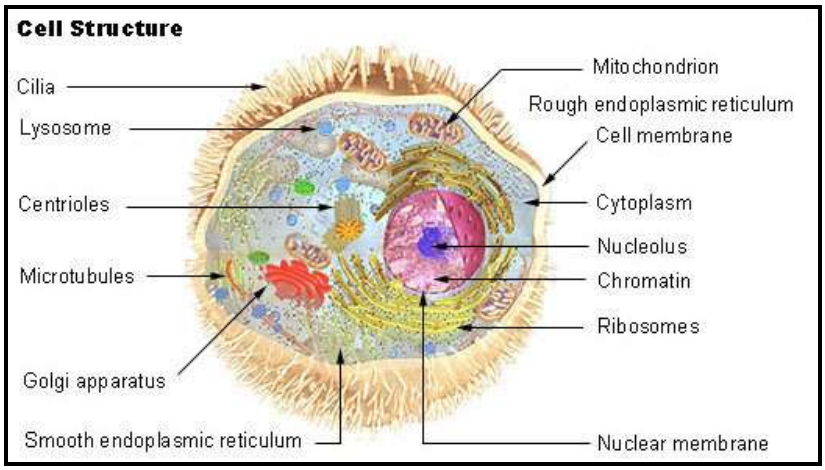

Fig. (1): Lysosomes inside the cell
(Samai et al., 2005).

Lysosomes are sub cellular organelles responsible for the physiologic turnover of cell constituents, containing catabolic enzymes requiring a low optimum ph to function.

These enzymes specifically (acid hydrolase) that break macromolecules down to peptides, aminoacids, mon-osacharides, nucleic acids and, fatty acids by endocytosis interiorization of extracellular material and autophagy digestion of intracellular component ***(Lango, 2006).***

Lacking of one of these enzymes leading to accumulation of these materials in lysosomes causing lysosomal storage disease.

There are more than 40 of LSD that are individually rare, but collectively common ***(Celia and Kaye, 2006).*** They have an incidence of approximately 1 in 7000-8000 live births.

These storage diseases describe a heritable group of rare heterogeneous human disorders characterized by the accumulation of undigested macromolecules intralysosomaly, which result in an increase in the size and number of these organelles and ultimately in cellular dysfunction and clinical abnormalities.

Lysosomal storage diseases are generally classified by the accumulated substrate and they include sphingolipidoses, glycoproteinoses, mucolipidoses, mucopolysaccharidoses (MPSs), and others.

The concept of lysosomal storage disease has been expanded to include deficiencies in lysosomal enzymes, deficiencies in the non catalytic lysosomal protein, and more general abnormalities in lysosomal functions occurring in the lysosomes ***(Parkinson et al., 2006)***.

Pathophysiology:

Recent advances in molecular genetics have shifted the focus both in gene products and gene themselves. The defective gene in most of these genetic diseases have been isolated and characterized and the specific mutations identified. At the gene level, genetic heterogenecity is complex despite similar phenotypes, biochemistry and enzyme defects. ***(Brady and Schiffmann, 2004).***

Manifestations:

Although these abnormalities result in substrate accumulation, the underlying mechanisms relating to the pathologic effect are not entirely clear, however, the distribution of the accumulating material does determine which organs are affected.

In particular, neurons that are incapable of cell division are commonly impaired because of undegraded material and lack of cell turnover, cells of the mononuclear phagocyte system are especially rich in lysosomes and so are frequently affected by lysosomal storage disease.

Lysosomal storage diseases may result in severe neurodegenerative phenotypes. Milder or later onset phenotypes have been identified and are related to residual enzyme activity. Such subtypes and variants show that even at low enzyme activity level (as low as 1-5% of normal) a

severe neurologic course can be modified into a milder, often nonneurologic phenotype ***(Brady and Schiffmann, 2004)*.**

Classification:

1. Sphingolipidoses (Gaucher disease, Nieman -pick)
2. Mucopolysaccharidoses (Hurler, Hunter, Sanfilippo, Morquio)
3. Glycogenoses (Pompe)
4. Neuronal ceroid lipofuscinoses
5. Mucolipidoses (I-cell disease).
6. Oligosaccharidoses (fucosidosis).
7. Glycoproteinosis (Mannosidosis, Sialidosis, Fucosidosis)

(Kunz et al., 2001)

Key to pathophysiology of lysosomal storage disorders:

Disease phenotype is a consequence of the type of substrate and its sites of turnover.

- Activated macrophage (Gaucher, Nieman -pick)
- Vascular endotheliam (Fabry)
- Muscle / heart (Pompe)
- Connective tissue (Mucopolysaccharidoses) ***(Lango, 2006).***

Physical finding:

Tachypnea, apnea, lethargy, hypertonicity, hypotonicity, hepatosplenomegally, ambiguous genetalia, jaundice, dysmorfic or coarse facial features, rashes or patchy hypopigmentation, ocular findings (cataract-lens dislocation or pigmentry retinopathy), intracranial hemorrhage, unusual odors ***(Ghosh et al., 2003).***

Testing:

In general, according to ***Parkinson-Lawrence et al.*** in ***2006***, immune assays provide a direct particular application for the early detection, diagnosis, and prognosis of those with lysosomal storage disorders.

Multiplexing of these assays may provide a platform to allow newborn screening for multiple lysosomal storage disorders.

Laboratory findings:

- Metabolic acidosis with increased anion gap.
- Primary respiratory alkalosis.
- Hyperammonemia, hypoglycemia, ketosis or ketonuria, low BUN - Hyperbilirubinemia, lactic acidosis, high lactate /pyruvate ratio, non-glucose-reducing substance in urine.
- Elevated liver function tests including PT and PTT.
- Neutropenia and thrombocytopenia ***(Lango, 2006).***

Diagnosis of lysosomal storage disorders:

- Specific disorders are suspected based on clinical presentation.
- Measurement of enzyme activity remains the gold standard for confirmation of diagnosis (the sample required might be different (WBC, fibroblast, serum).
- Mutation screening is efficient in certain populations (Gaucher in Ashkenazi) and is essential for carrier detection.
- Prenatal diagnosis is available.
- Newborn screening in development using multiplex MS/MS multiplexed immune-quantification of a panel of lysosomal proteins ***(Lango, 2006).***

The multiplexed immune-quantification assay of 11 different lysosomal proteins for the identification of individuals with LSD have been developed using blood – spots ***(Celia and Kaye, 2006).***

New development in 2005-2007:

Therapy is increasingly promising, albeit expensive. Enzyme replacement therapy appears extraordinarily effective for patients with Gaucher disease type 1 and 3, Fabry disease, and Hurler-scheie.

In persons with Gaucher disease, a chemokine, CCL18, has been identified as a biomarker for clinical development that reflects disease severity and treatment responsiveness ***(Fukuda et al., 2007).***

Additional acid alpha-glucosidase deficiency has shown to be helpful for Pompe disease ***(El Dib and Pastores, 2007).***

Idursulfase for the treatment of Mucopolysaccharidosis II (Hunter syndrome) has been shown to help abate this disease and is now on the market in the United States and the European Union ***(Clarke, 2008).***

GAUCHER DISEASE

Historical review:

Philipe Gaucher had described Gaucher disease as a lysosomal storage disorder by identifying the characteristic Gaucher cell in the spleen of a patient diagnosed to have lymphoma in 1882, and its familial nature was recognized by ***Brill et al. (1904).***

In ***1927, Oberling et al.,*** had discovered the neurologic component of Gaucher disease, which is more common amongst the childhood forms.

In ***1960s, Brady and colleagues*** at the National Institute of Health in the USA made major contributions to the understanding of this disease by analyzing the metabolic defect, leading to the cloning of the gene by ***Ginns et al.***

In 1984, American workers, including Gabrowski and Pastores, have made major advances in helping patients with treatment of this disease using enzyme replacement therapy, which has been available now for over 10 years ***(Baranouva, 2007).***

Definition:

Gaucher disease occurs when certain harmful fatty substances build to excessive level in liver, spleen, lungs, bone marrow and, less commonly, brain.

This accumulation of fatty materials in tissues interfere with the normal functioning of organs, and may cause organ enlargement and bone pain.

Gaucher disease is the most common lipid storage disease where abnormal amounts of lipids called "glycosphingolipids" are stored in special cells of the reticuloendothelial system called Gaucher cells ***(Orvisky et al., 2002).***

Gaucher disease is most common in Eastern and Central European (Ashkenazi Jews). It can occur at any age in life and affects males and females approximately equally.

Pathophysiology:

The disease is caused by a defect in the housekeeping gene lysosomal gluco-cerebrosidase (also known as B-glucosidase) on the first chromosome (1q21).

The enzyme is a 55.6 KD, 497 amino acids long proteins that catalyses the breakdown of glucocerebroside, a cell membrane constituent of red and white blood cells.

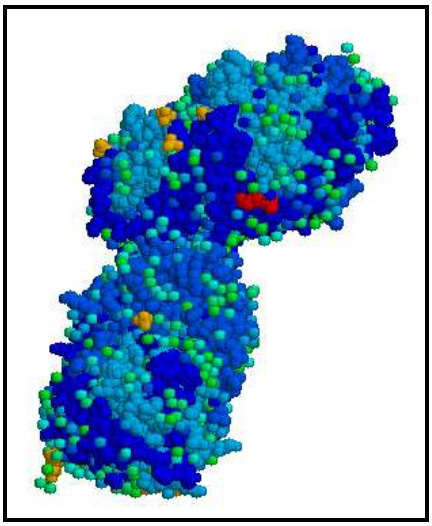

Fig. (2): B. glucosidase enzyme
(Landgren et al., 2007).

The macrophage that clear these cells are unable to eliminate the waste products, which accumulate in fibrils, and turn into Gaucher cell, which appear on light microscopy containing crumpled-up paper ***(Landgren et al., 2007).***

Different mutations in the B-glucosidase determine the remaining activity of the enzyme, and to a large extent, the phenotype.

In the brain, glucocerebroside accumulates due to the turnover of complex lipids during brain development and the formation of the myelin sheath of nerves.

Researches suggest that heterozygotes for particular acid B-glucosidase mutations are at an increased risk of Parkinson's disease.

A study of 1525 Gaucher patients in the United States suggested that while cancer risk is not elevated, particularly malignancies (non-Hodgkin lymphoma, melanoma, and pancreatic cancer), But it could occurre at a 2-3 times higher rate ***(Landgren et al., 2007).***

The pathologic hallmark of Gaucher disease is the Gaucher cell in the reticuloendothelial system, particularly in the bone marrow.

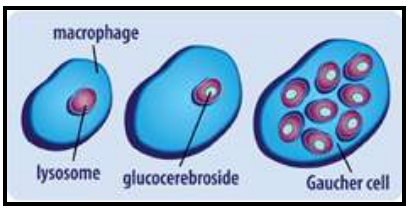

Fig. (3): Development of Gaucher cell ***(Aerts et al., 2008)***.

Typical Gaucher cells are large round or polyhydral phagocytes that are 20-100mm in diameter. Classically the nucleus is pushed off to one side and the remainder of the cell is filled with abnormal lipids.

Gaucher cells contain one or more small eccentrically placed nuclei and a pale striated cytoplasm that resembles wrinkled tissue paper or crumpled silk resulting from intracytoplasmic inclusions ***(Schoonhoven et al., 2007).***