75° CONGRESSO NAZIONALE

FIMG

Metis

Potenziare la medicina generale per migliorare l'Active Ageing

1-6 ottobre 2018

Complesso Chia Laguna - Domus de Maria (CA)

La Malattia di Gaucher

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Disclosures

Member of scientific board for:

- Novartis
- Sanofi/Genzyme
- Celgene
- La Jolla
- CRISPR
- Vifor

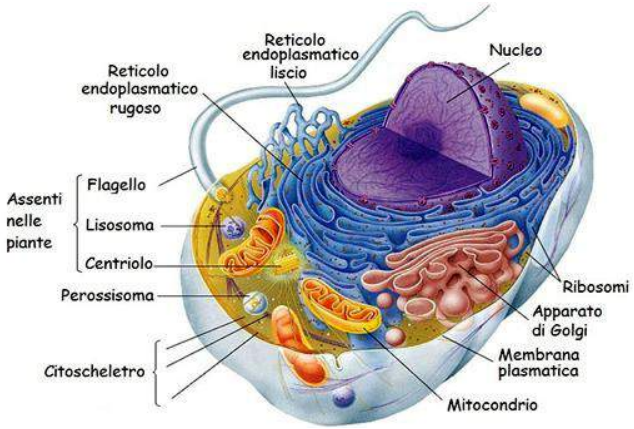
Lysosomal Storage Disorders (LSDs)

- LDSs are a heterogeneous group of inherited diseases resulting from the deficiency in one or more enzymes or transporters that normally reside within the lysosomes
- They are characterized by progressive accumulation of uncleaved lipids, glycoproteins and/or glycosaminoglycans in the lysosomes
- The consequences are organ damages and several forms have severe liver and spleen enlargment

Malattie da accumulo lisosomiale

Prevalenza stimata di circa 1:8000 nati vivi

Classe di malattie metaboliche causate da mutazioni codificanti per proteine fondamentali per la funzione lisosomiale



Schultz ML, Trends in Neurosciences, 2011,34,8, 401-410.

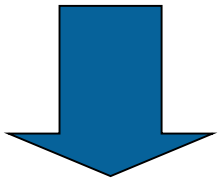
Malattie da accumulo lisosomiale

Attualmente si conoscono più di 45 malattie lisosomiali

Monogeniche, ereditarietà autosomica recessiva o X-linked

Patogenesi, da difetto genetico per:

- uno o piu' enzimi lisosomiali specifici
- proteine di attivazione
- proteine di membrana



Attività enzimatica deficitaria

Malattie da accumulo lisosomiale

Attività enzimatica deficitaria

↓

Accumulo progressivo del relativo substrato

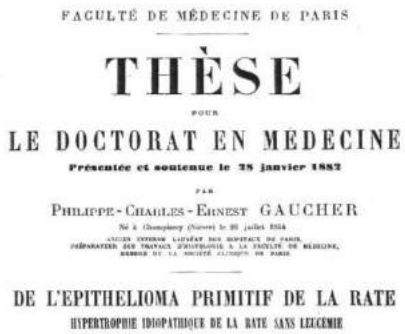
↓

Interferenza sulla normale attività cellulare

↓

Morte cellulare

Meikle PJ, JAMA, 1999, 281(3), 249-254.



FACULTÉ DE MÉDECINE DE PARIS

THÈSE

POUR

LE DOCTORAT EN MEDECINE

Présentée et soutenue le 28 janvier 1882

PAR

PHILIPPE-CHARLES-ERNEST GAUCHER

DE L'EPITHELIOMA PRIMITIF DE LA RATE

HYPERTROPHIE IDIOPATHIQUE DE LA RATE SANS LEUCÉMIE

- It is the most common inherited lysosomal storage disease
- Gaucher Disease is caused by inherited deficiency in acid beta-glucosidase (glucocerebrosidase, GBA)
- Leads to glucocerebroside accumulation in lysosomes of macrophages
- Glycolipid laden cells (Gaucher cells) infiltrate organs to cause multisystem disease

Beutler & Grabowski 2001. In: Scriver et al eds The metabolic and Molecular Bases of Inherited Disease. 8th Ed NY: Mc Graw-Hill: 3635-3668

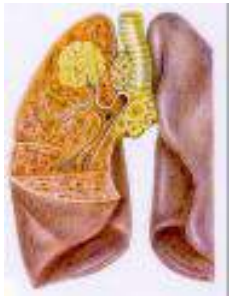
Gaucher Disease: Clinical Types

Clinical Features	Type 1	Type 2	Type 3
Age at onset	Childhood/ Adulthood	Infancy	Childhood
Splenomegaly	+ → +++	++	+ → +++
Hepatomegaly	+ → +++	++	+ → +++
Skeletal disease/ bony crises	- → +++	--	++ → +++
Primary CNS disease	Absent	+++	+ → +++ (1st to 5th decade)
Lifespan	6 to 80+ years	~2 years	2 to 60 years
Ethnicity/	Panethnic Ashkenazi Jewish	Panethnic	Panethnic Norrbottnian
Frequency	1/60000 ~ 1/500 to 1/1,000 (AJ)	< 1/100,000	< 1/50,000

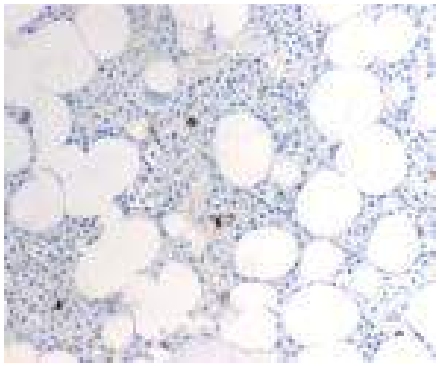
Organs Involvement

Enzyme deficiency

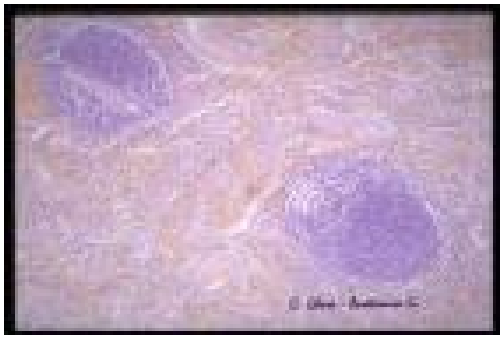
Macrophages



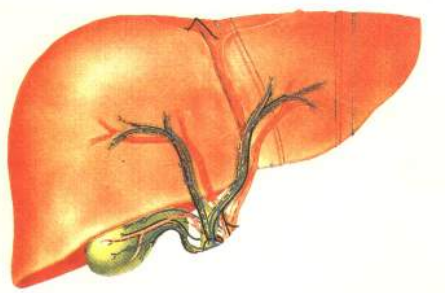
Lungs
Alveolar macrophages)



Bone marrow



Spleen



Liver (Kuppfer cells)

Bones

Patologia multidisciplinare

Chirurgo

Ematologo

Reumatologo

Medico di famiglia

Internista

Malattia di Gaucher

Ortopedico

Radiologo

Ginecologo

Splenomegaly

- Present in more than 90% of GD patients at diagnosis
- Defined as spleen greater than 0.2% of total body weight in Kg

- Because of high incidence of GD in Ashkenazim, GD should be considered in any individual of Ashkenazi origin presenting with mild, moderate or severe splenomegaly

- However... the absence of splenomegaly does not exclude GD

Kaplan et al 2006 Arch Pediatr Adolesc Med;160(6):603-8
Pastores et al 2004 Semin Hematol;41(4 Suppl 5):4-14

Caso clinico, AP, 39 aa, M

Il paziente si reca in visita ambulatoriale per richiedere una prescrizione di farmaci antidolorifici

Caso clinico, AP, 39 aa, M

In anamnesi familiare:

- padre e madre ipertesi
- madre portatrice di deficit di G6PD
- una sorella in buona salute
- non familiarità per talassemia

Caso clinico, AP, 39 aa, M

In anamnesi patologica remota:

- Diagnosi di G6PD in età infantile
- Verosimile ittero neonatale
- Cefalalgico

Caso clinico, AP, 39 aa, M

EO:

- fegato a 3-4 cm dall'arcata costale in IP
- Milza in FIS

Caso clinico, AP, 39 aa, M

Caso clinico, AP, 39 aa, M

EO:

- fegato a 3-4 cm dall'arcata costale in IP
- Milza in FIS

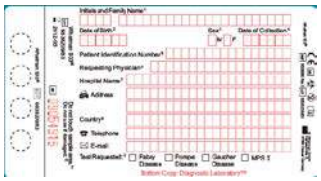
EE:

- Hb 11.6 g/dl, MCV 79.8 fl, PLT 70000
- Ferro: 58 mcg/dl, transferrina 304 mg/dl, ferritina 799 ng/ml
- Gilbert: genotipo "nella norma"

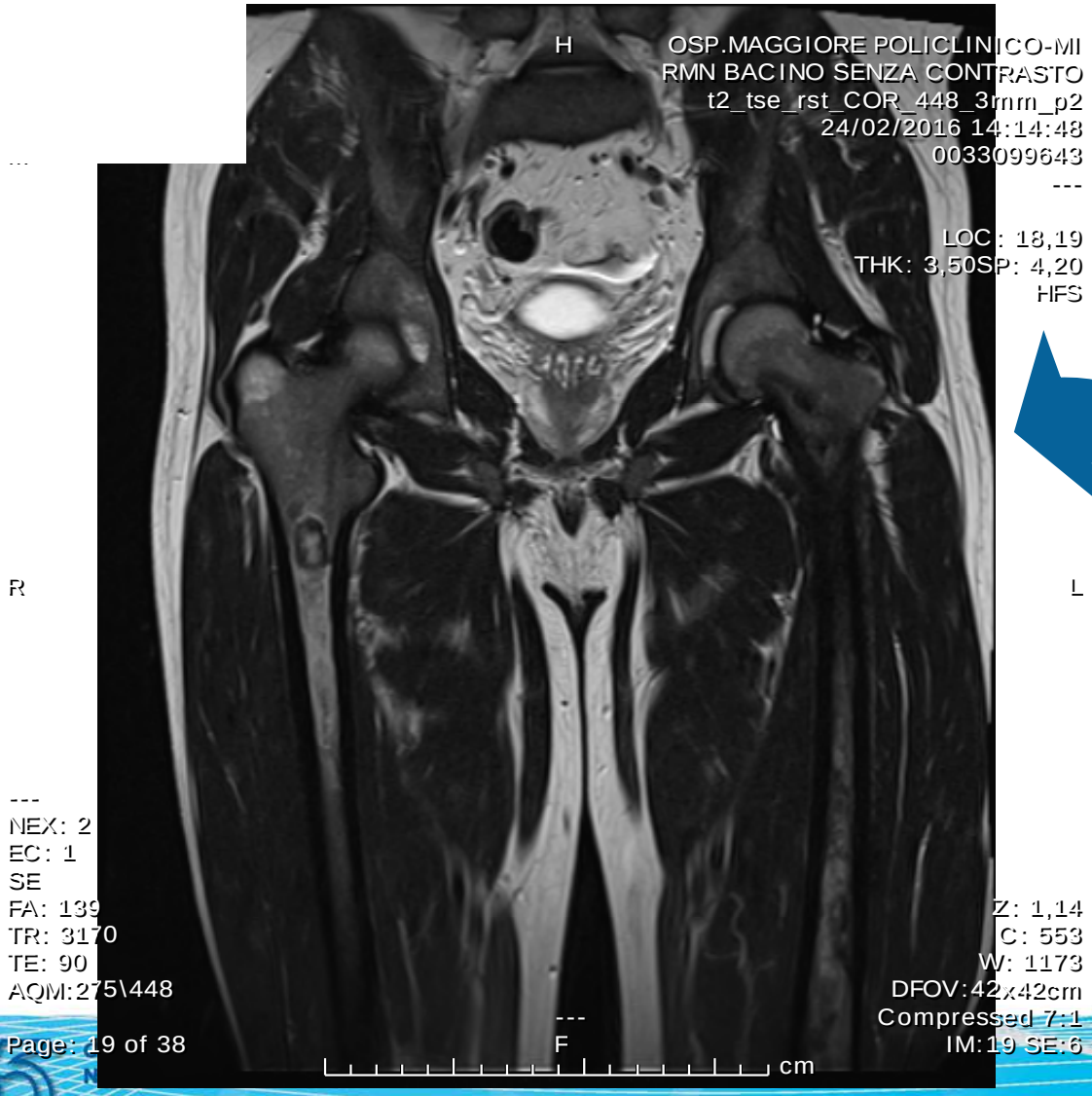
Caso clinico, AP, 39 aa, M

Splenomegalia

- Eco addome: epatomegalia, milza diam AP 26 cm
- Dosaggio G6PD: ridotto
- Indagini per talassemia
  - HPLC: nella norma
  - Indagine molecolare ed MLPA: ndp
- Studio delle membrane eritrocitarie: neg
- Ricerca mut.HFE: negativa
- DBS per Malattia di Gaucher: POSITIVO



Caso clinico, AP, 39 aa, M

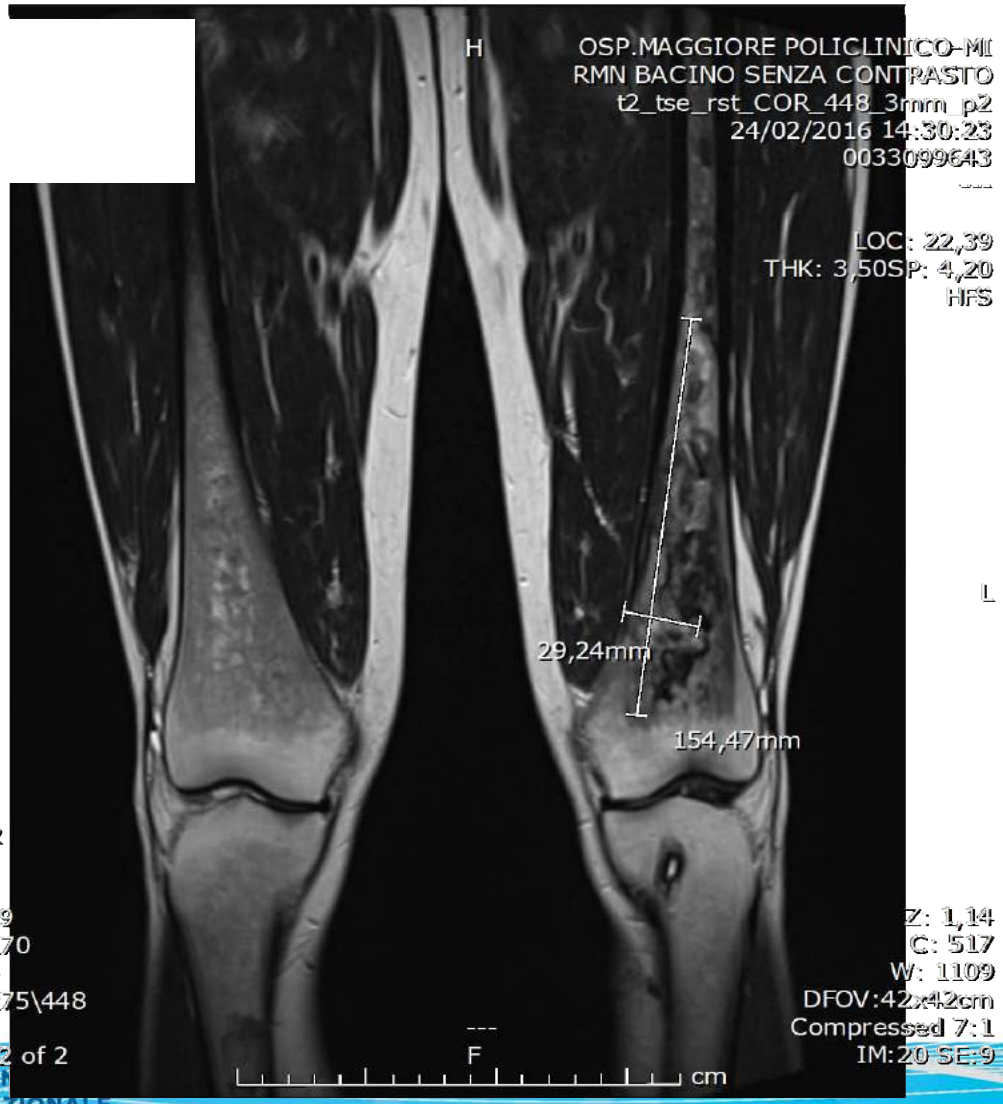


RMN femori

T2

…..ma non solo questo

Caso clinico, AP, 39 aa, M



RMN femori

T2

Key manifestations in adult Gaucher type 1

- **Splenomegaly:** abdominal discomfort, satiety
- **Thrombocytopenia:** tendency to bleed (+/- coagulation abnormalities)
- **Anaemia:** chronic fatigue
- **Leucopenia:** increased susceptibility to infections (+/- compromised neutrophil function)
- **Bone disease:** pain, acute bone crises, avascular necrosis, bone deformation, osteopenia, osteoporosis, fractures, joint collapse
- **Hepatomegaly:** often affecting liver function

Presenting Signs

- Presenting signs and symptoms often related to the haematological manifestations of disease:
  - Thrombocytopenia
  - Anaemia
  - Bleeding
- Other haematological signs may include
  - Hyperferritinemia
  - Vitamin B12 deficiency
  - MGUS
  - Coagulopathies
  - Increased risk of haematological malignancy

Hughes et al 2007 Br J Haematol:138(6):676-86

Gaucher Disease Treatment
Milestones

1985: Glucocerebrosidase gene (*GCB*) cloned[1] and mapped to chromosome 1q21[1,2]

First recombinant human glucocerebrosidase ERT approved in US (imiglucerase) in 1994 and in EU in 1997

2003: IND filed for GZ-112638 (Cerdelga)

2010: FDA, EMA approval of VPRIV

2014: Approval of Cerdelga in US for adults with GD1

2015: Approval of Cerdelga in EU for adults with GD1

1980 | 1990 | 2000 | 2010 | 2014 | 2015

1983: First patient with GD1 treated at NIH with glucocerebrosidase purified from human placenta

1991: First placental-derived glucocerebrosidase ERT approved in US and EU (alglucerase)

2003: First SRT approved (EU SmPC: Zavesca may be used only in the treatment of patients for whom enzyme replacement therapy is unsuitable)

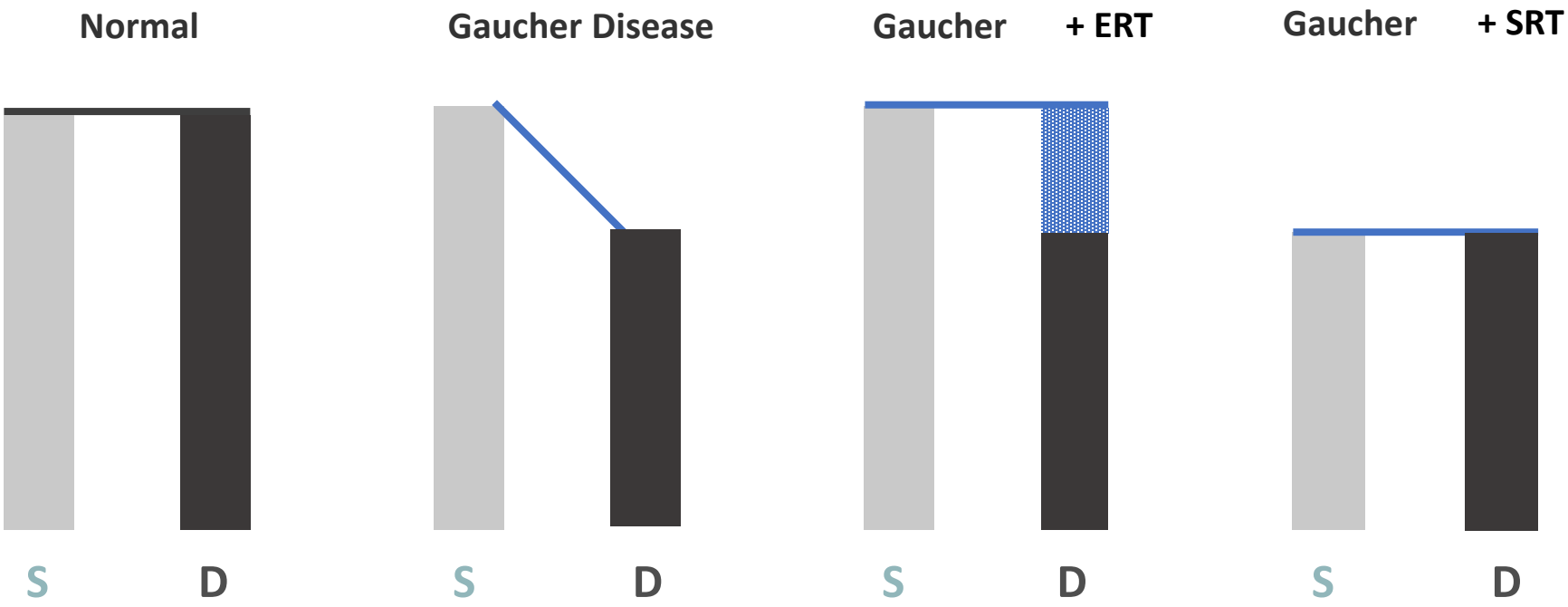
More than two decades later…

1. Sorge et al. *PNAS*.1985:82:7289-7293.
2. Ginns et al. *PNAS* 1985;82:7101-7105.

GD1=Gaucher disease type 1; IND=Investigational New Drug; ERT= enzyme replacement therapy; SRT=substrate reduction therapy

Gaucher Disease Treatment
Two Approaches: ERT and Substrate Reduction

Restoring a balance between substrate synthesis and degradation



Synthesis (S) & Degradation (D) of glucosylceramide

Graphics are intended for illustrative purposes only.

Adapted from Shayman. *Drugs Future*. 2010:35:613-620.

ERT=enzyme replacement therapy; SRT=substrate reduction therapy.

Grazie per l'attenzione