Il paradigma di una malattia rara: la Malattia di Gaucher

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DALLA PRESTAZIONE ALLA PERFORMANCE
74° Congresso Nazionale
2-7 ottobre 2017

Disclosures

Member of scientific board for:

- Novartis
- Sanofi/Genzyme
- Celgene
- La Jolla
- Roche

Rare Diseases

✓ Rare diseases, including those of genetic origin, are life-threatening or chronically debilitating diseases which are of such low prevalence that special combined efforts are needed to address them

✓ Low prevalence is taken as prevalence of less than 5 per 10 000 persons in the European Union.

European Rare Diseases Task Force

Rare Diseases

✓ It is estimated that between 5 000 and 8 000 distinct rare diseases exist today, affecting between 6% and 8% of the population in total - in other words, between 27 and 36 million people in the European Union

✓ The United States definition is very similar to the European one. In the US an orphan or rare disease is generally considered to have a prevalence of fewer than 200 000 affected individuals.

Mr S.B, age 36 yrs, officier in a library. Married

- Active sportman, had lack of energy, tiredness since few months leading to sport activity restriction

- No other symptoms but mild, occasional peripheral sensory loss
- Family History: southern italian origin. Parents apparently in good health. 3 brothers, 2 sisters

More clues……

- Hb: 12.5 g/dl ; MCV: 81 fl
- Platelets: 88/10^9l

- AST: 27 U/L, ALT: 47 U/L, gGT: 35 U/L
- Tot. Bilirubin: 1.7 mg/dl, Unconj: 1.3 mg/dl
- HCV, HbsAg: negative

- Iron:84 mg/dl; Transferrin saturation:30 %;
- Ferritin: 1400 ng/ml;

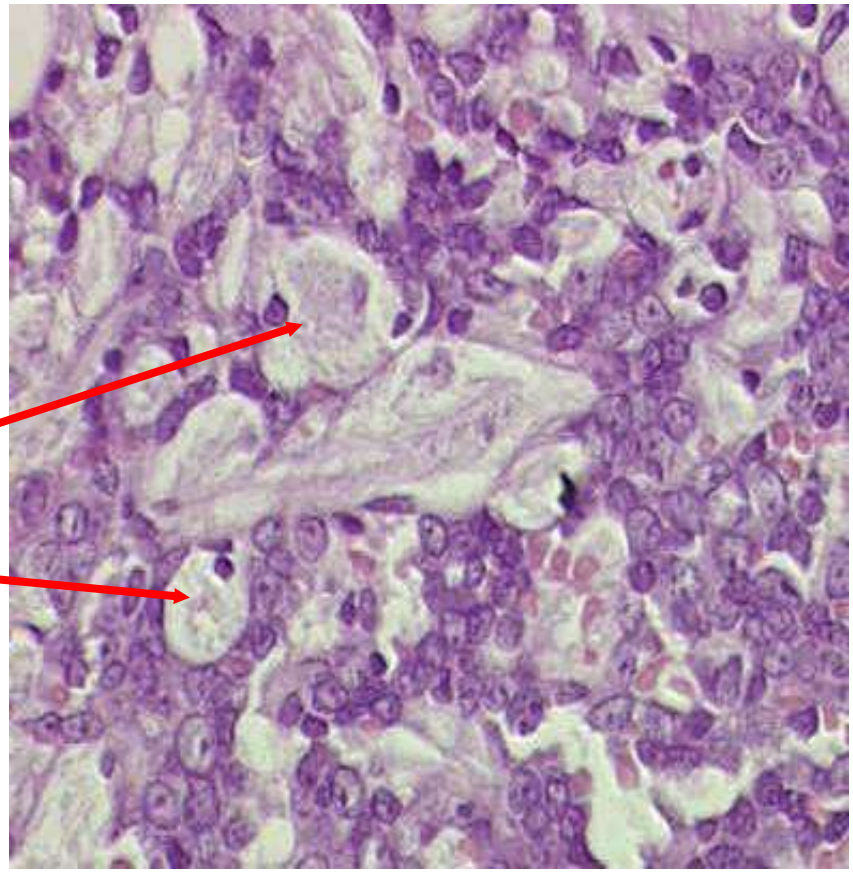
- Blood film: normo/microcytic cells; poichylocitosis
- Hb pattern; G6PD activity: normal

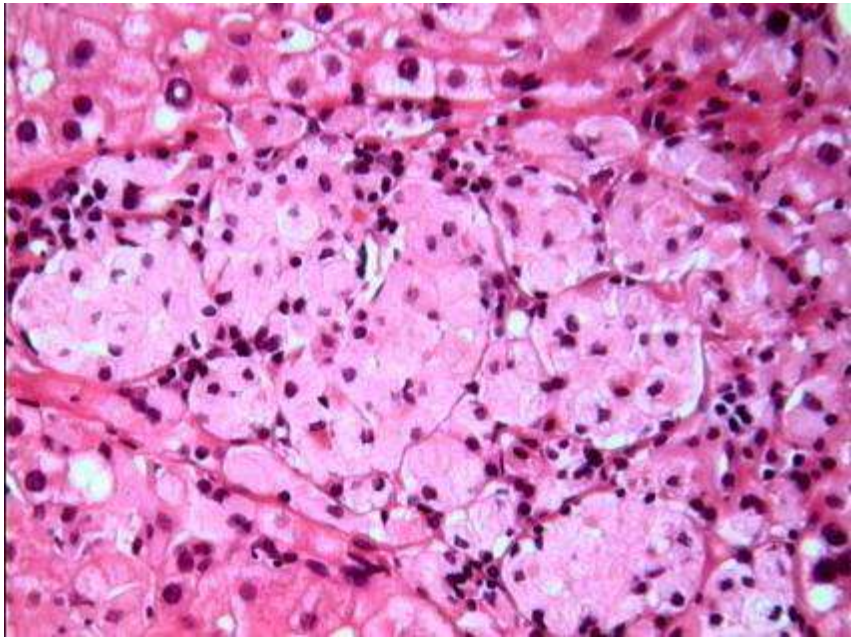
Liver enlargement (4 cm); spleen enlargement (3 cm)

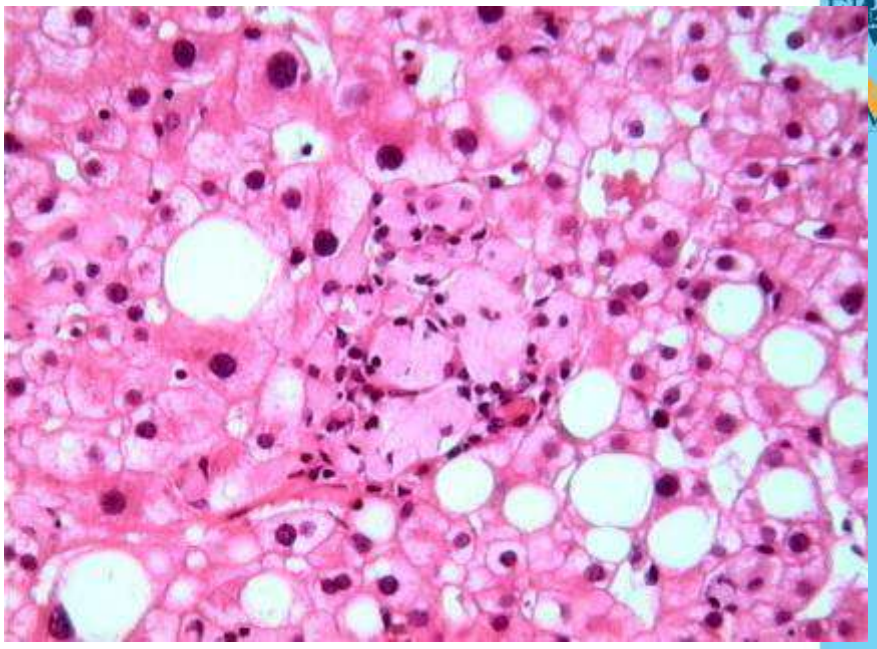
Suspected diagnosis

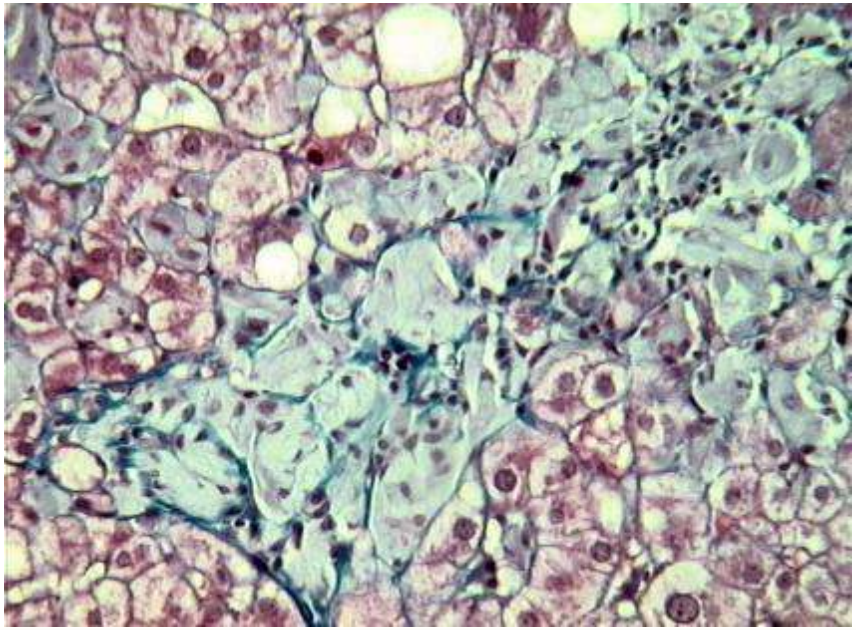
- Viral neurophaty (neurologist)
- Mononucleosis
- Hepatitis/Cirrhosis (Hepatologist)
- Lymphoma (Hematologist)

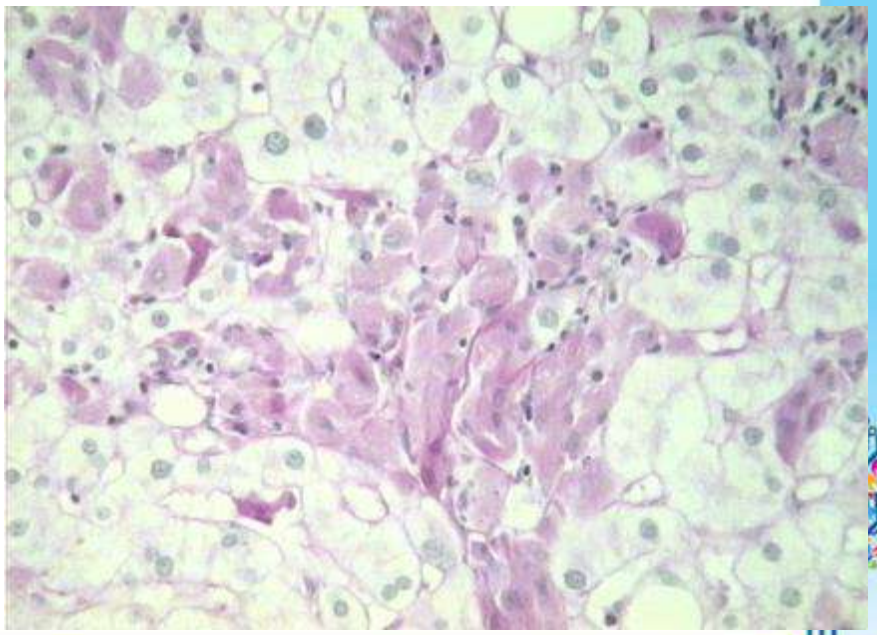
Gaucher like cells?



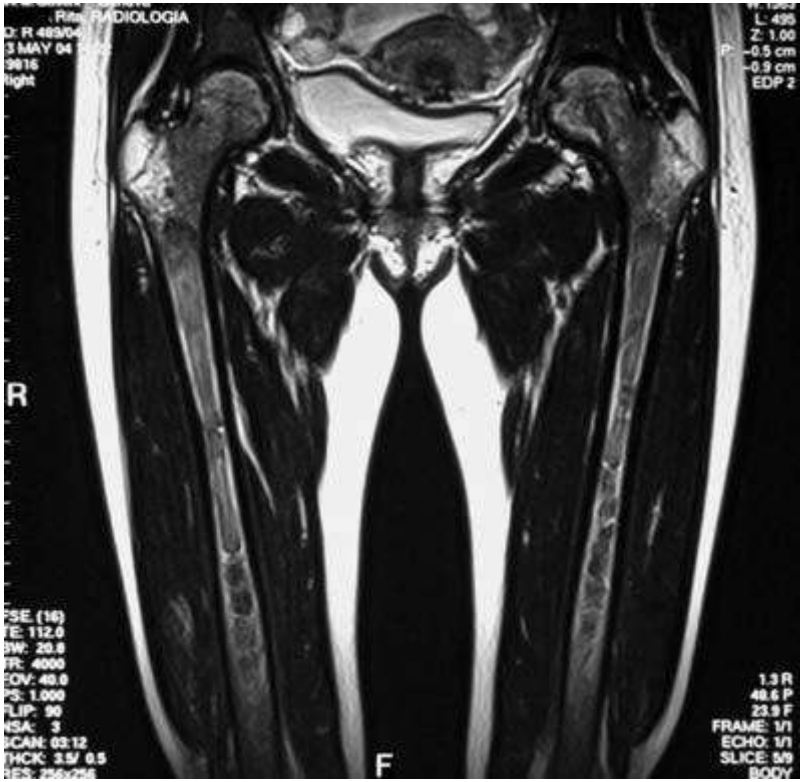


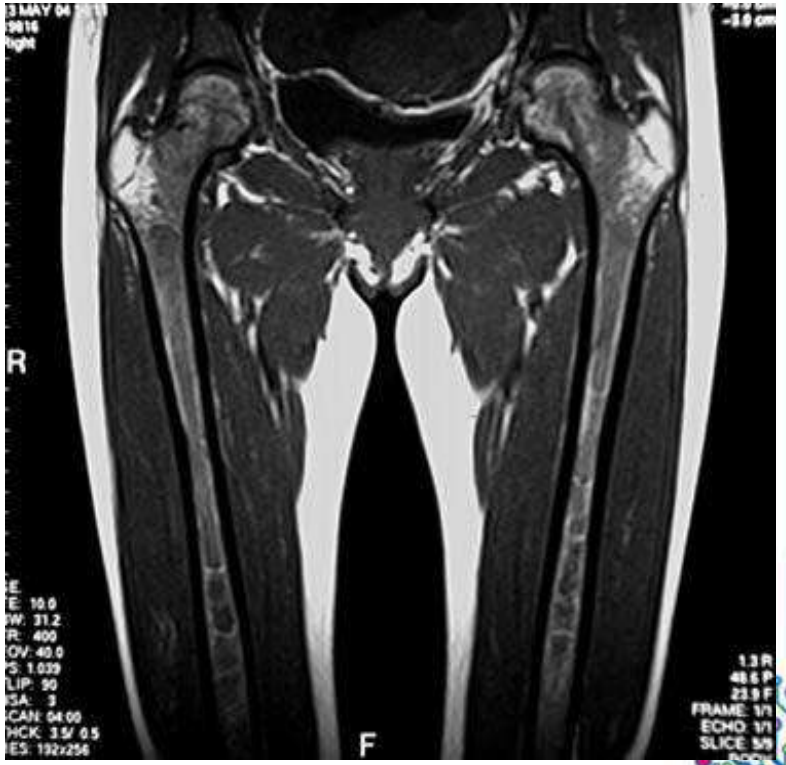






Keck School staging :1a





Mr S.B, age 36 yrs,
officier in a library. Married

- More than 1 year before diagnosis was made
- He viseted 4 different specialists
- He underwent 2 invasive exams (BM, Liver biopsy)

Malattia di Gaucher

AS, 49 aa

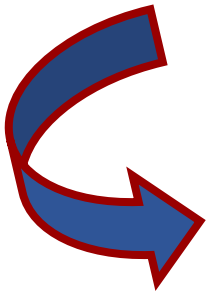
✓ dall'infanzia sino all'adolescenza ha portato un "corsetto" (non sa documentare le motivazioni), senza problemi di crescita

✓ anamnesi silente fino al 2001, quando nel 2001.. **blocco meniscale** durante attività fisica in bicicletta

✓ **intervento in artroscopia** senza problemi di sanguinamento (agli EE pre-operatori **PLT 60.000**)

AS, 49 aa

- ✓ nel 2005 intenso dolore lombare ed all'anca destra
- ✓ Rx anca destra: necrosi asettica della testa femorale destra



Indicazione chirurgica per protesi d'anca

AS, 49 aa

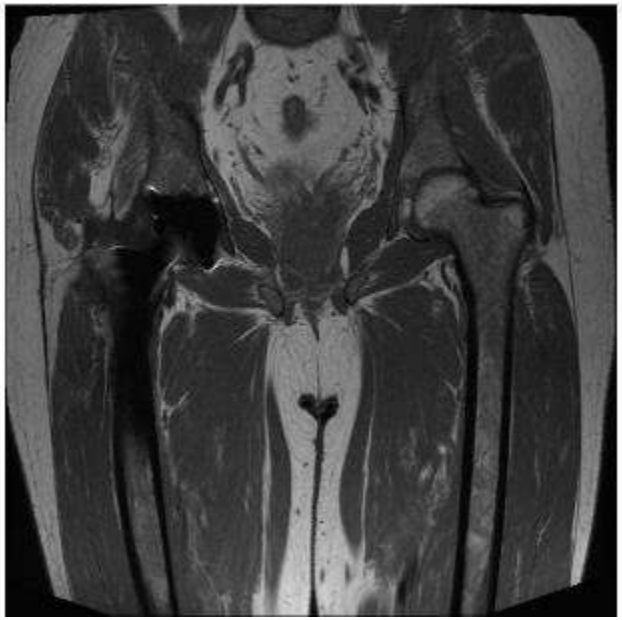
- GB 10900/mm^3 ;
- GR 4.480/mm^3
- Hb 14.7 g/dl
- MCV 95.3 fl

Ferritina 1393 ng/ml

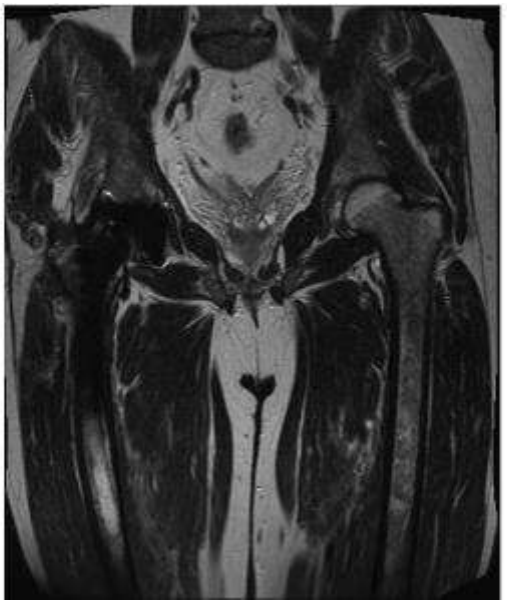
- AST 21 U/L, ALT 18 U/L, gGT 31 U/L
- Bilirubina tot 0.51 mg/dl, ind <0,01 mg/dl
- Dosaggio di folati e vitamina B12 nella norma

Ptl 89000/mm^3

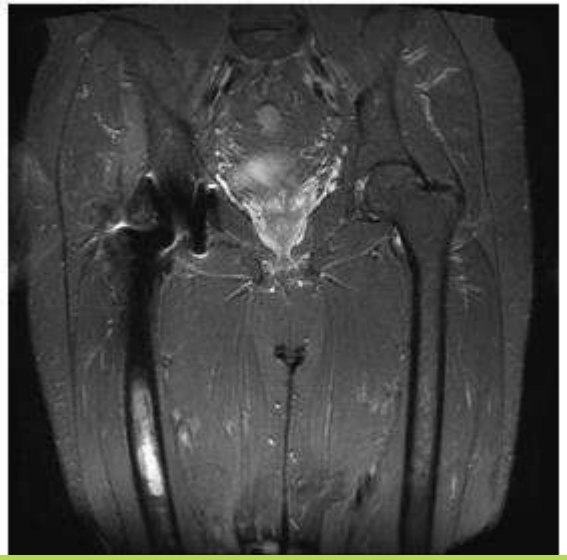
RMN



T1



T2



STIR

AS, 49 aa, M

Protesi d'anca
(necrosi asettica testa femorale)

Piastrinopenia

Problemi ossei nell'infanzia

Malattia di Gaucher

GP/Internists *key in diagnosis*

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):676-8

Malattia di Gaucher

E’ una malattia autosomica recessiva caratterizzata dalla presenza di due alleli mutati per il gene della glucocerebrosidasi, localizzati nella regione q21 del cromosoma 1.

Tale alterazione comporta un accumulo di glucocerebroside all’interno di macrofagi specialmente nel sistema reticolo-endoteliale che possono infiltrare differenti organi quali il fegato, la milza, il midollo osseo ed il polmone.

Patologia multidisciplinare

Chirurgo

Ematologo

Reumatologo

Medico di famiglia

Internista

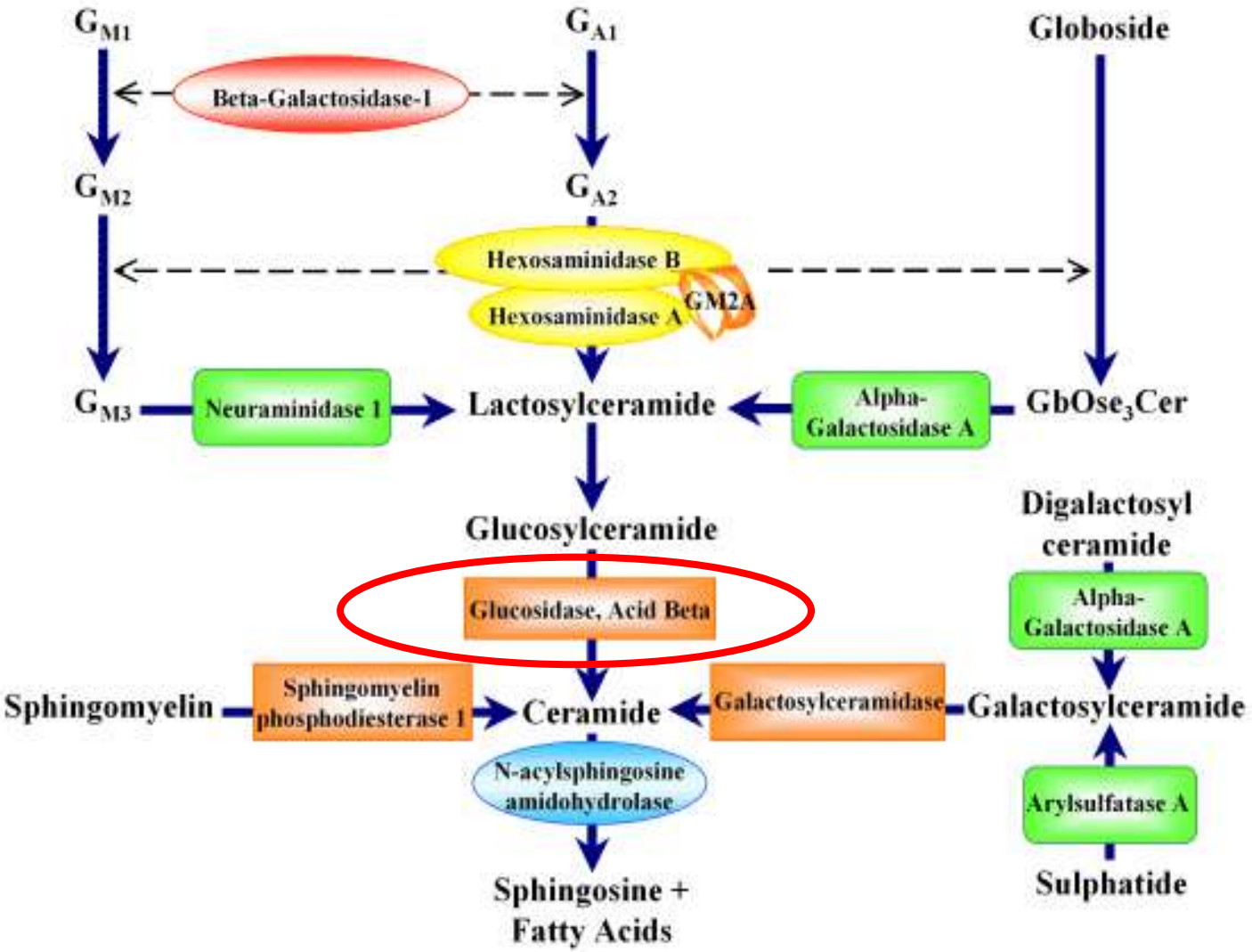
Malattia di Gaucher

Ortopedico

Radiologo

Ginecologo

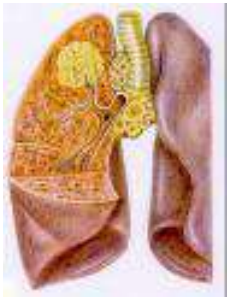
Malattia di Gaucher



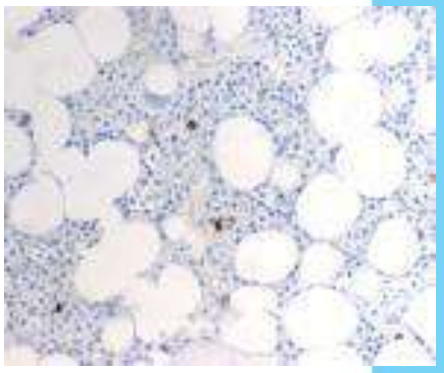
Coinvolgimento d'organo

Deficit enzimatico

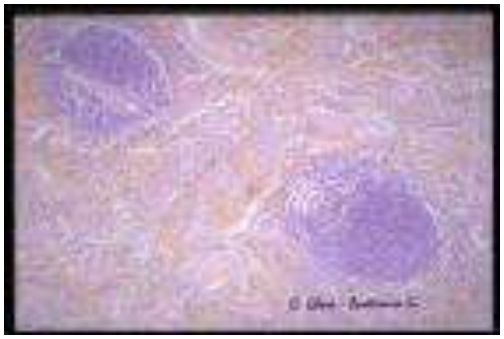
Macrofagi



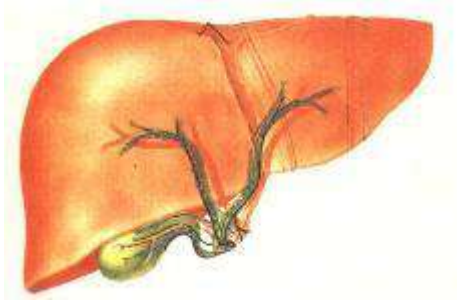
Polmoni
(macrofagi alveolari)



Midollo osseo



Milza (macrofagi tissutali)



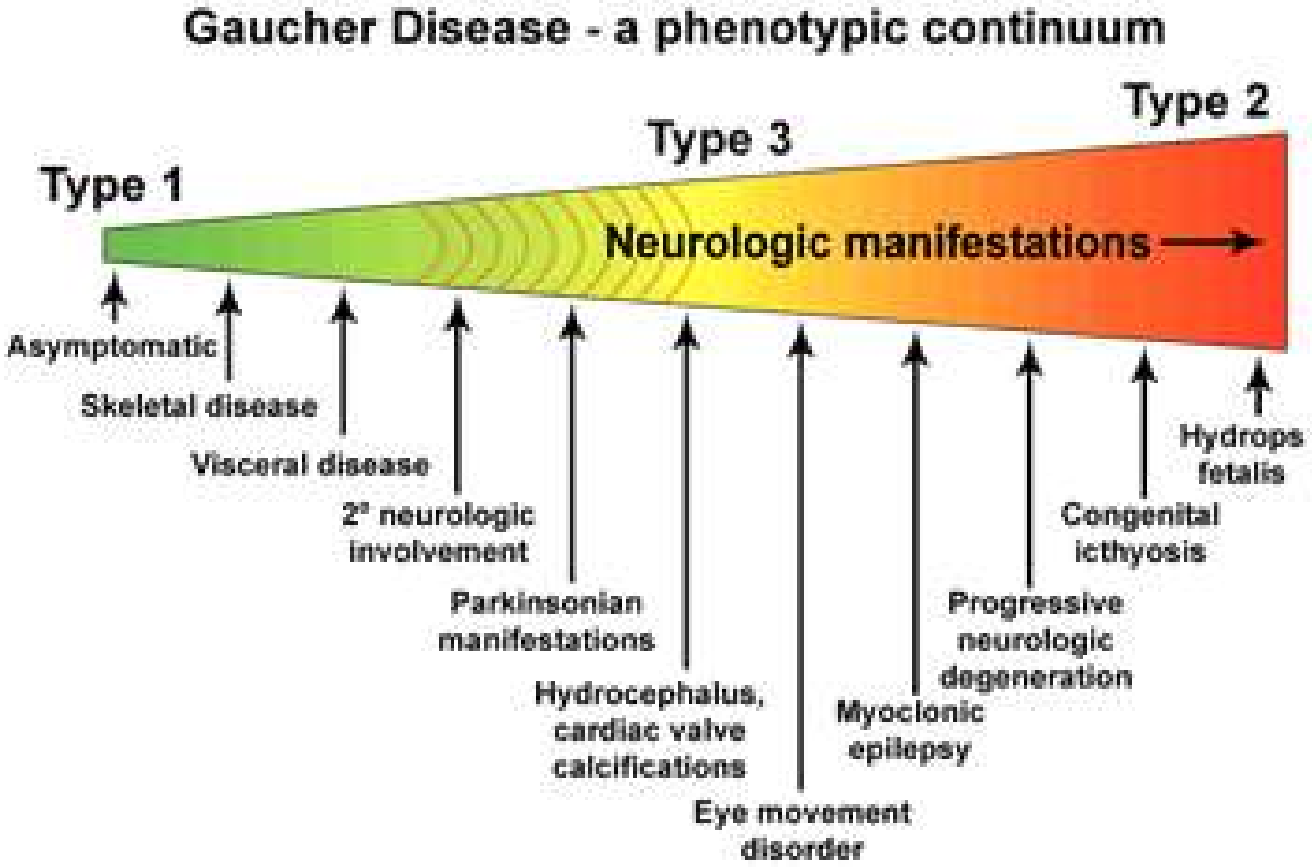
Fegato (cell. Kuppfer)

Osso (osteoclasti)

Manifestazioni cliniche

CARATTERISTICA	TIPO I	TIPO II	TIPO III
NOME DESCRITTIVO	Non neuropatica (forma adulta o cronica)	Neuropatica acuta (forma infantile)	Neuropatica subacuta (forma giovanile)
INCIDENZA	Da 1 a 40000 a 1 a 60000 (da 1 su 450 a 1 su 1500 negli ebrei Askenazi)	< 1 su 100000	Da < 1 su 50000 a < 1 su 100000
ETNIA	Pan-etnica (ebrei Askenazi)	Pan-etnica	Pan-etnica (Svedesi Norrbottniani)
ETA' INSORGENZA	qualsiasi età	Neonatale	Pediatrica
ASPETTATIVA DI VITA	Da 6 a 80 anni o più	< 2 anni	Da 2 a 60 anni
COINVOLG. NEUROL.	--	+++	+/+++ (progressivo)
EPATOSPLENOMEGALIA	+/+++	++	+/+++
ANOM. EMATOLOGICHE	+/+++	+++	+/+++
COINV. SCHELETRICO	+/+++	--	-/+++

Manifestazioni cliniche



Patients with Gaucher disease can have a spectrum of symptoms, ranging from mild to severe neurological effects. The classic categories of types 1, 2 and 3 have blurry edges along this continuum.

Complicanze ematologiche e viscerali alla diagnosi

	Italy	European area
Patients enrolled	**121**	**1761**
Anaemia†, n (%)	**n=45**	**n=646**
Yes	15 (33)	193 (30)
No	30 (67)	453 (70)
Thrombocytopenia‡ (platelet count, x 10^3/mm^3) [non-splenectomized patients only], n (%)	**n=40**	**n=612**
Mild or none (≥120)	17 (43)	229 (37)
Moderate (60 to <120)	17 (43)	288 (47)
Severe (<60)	6 (15)	95 (16)
Splenomegaly (Spleen Volume in Multiples of Normal), n (%)	**n=7**	**n=282**
Mild or none (≤5)	0 (0)	16 (6)
Moderate (>5 to ≤15)	3 (43)	166 (59)
Severe (>15)	4 (57)	100 (35)
Hepatomegaly (Liver Volume in Multiples of Normal) , n (%)	**n=7**	**n=279**
Mild or none (≤1.25)	0 (0)	109 (39)
Moderate (>1.25 to ≤2.5)	5 (71)	135 (48)
Severe (>2.5)	2 (29)	35 (13)

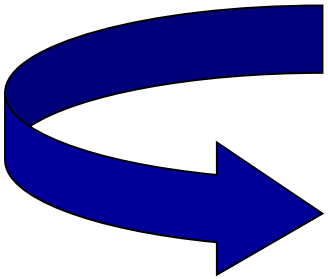
Data from Gaucher Registry

Complicanze ossee alla diagnosi

	Italy		European area	
Patients Enrolled	**n=121**		**n=1761**	
Bone Pain, n (%)	**n=35**		**n=533**	
Absent	25 (71)		338 (63)	
Present	10 (29)		195 (37)	
Very Mild	2 (20)		34 (17)	
Mild	5 (50)		62 (32)	
Moderate	1 (10)		41 (21)	
Severe/Extreme	0 (0)		21 (11)	
Not Specified	2 (20)		37 (19)	
Prior Bone Crisis, n (%)	**n=30**		**n=472**	
Absent	29 (97)		446 (94)	
Present	1 (3)		26 (6)	
Radiologic Bone Disease, n (%)				
Evidence of Any Bone Disease	**n=26**		**n=309**	
Absent	12 (46)		56 (18)	
Present	14 (54)		253 (82)	
Type of Bone Disease Reported	Any Data Available, n	Abnormality Present, n(%)	Any Data Available, n	Abnormality Present, n(%)
Avascular Necrosis	8	1 (13)	171	25 (15)
Erlenmeyer Flask Deformity	19	3 (16)	216	145 (67)
Fractures	14	0 (0)	152	12 (8)
Infarction	16	1 (6)	166	20 (12)
Lytic Lesions	15	0 (0)	149	9 (6)
Marrow Infiltration	10	8 (80)	126	94 (75)
Osteopenia	23	12 (52)	192	70 (36)
Decreased Bone Mineral Density (lumbar spine DXA z-score†), n (%)	**n=0**		**n=86**	
Mild or None (> –1)	0 (0)		44 (51)	
Moderate (> -2.5 to ≤ –1)	0 (0)		35 (41)	
Severe (≤ –2.5)	0 (0)		7 (8)	
Pediatric Growth Retardation, n (%)	**n=20**		**n=310**	
Observed	4 (20)		99 (32)	
Expected‡	1 (5)		16 (5)	

Data from Gaucher Registry

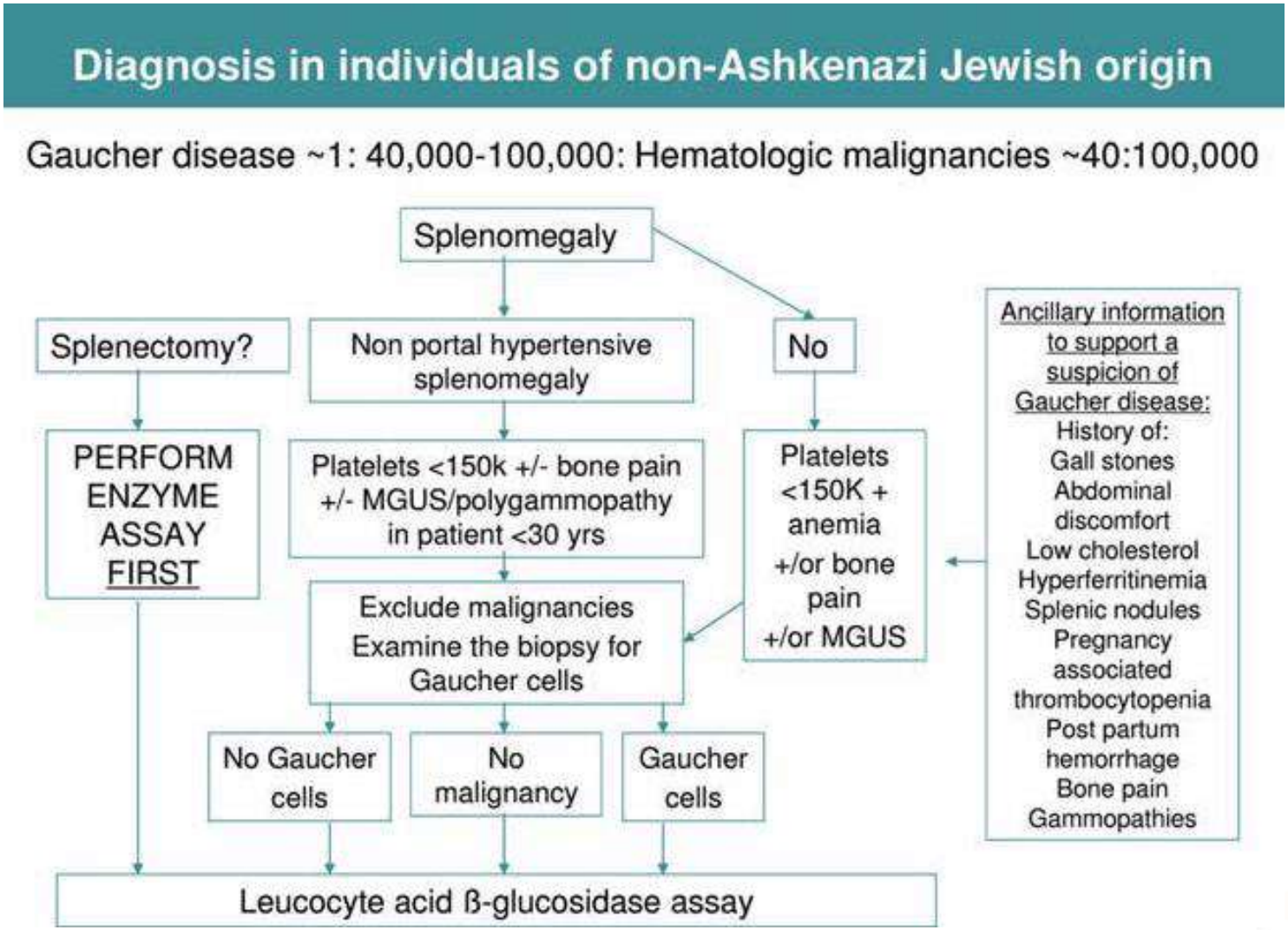
Età alla diagnosi



Patients Enrolled	5710
Disease Type*, n (%)	**n=5458**
Type 1	5005 (92)
Type 2	62 (1)
Type 3	391 (7)
Sex, n (%)	**n=5710**
Males	2669 (47)
Females	3041 (53)
Age at Diagnosis† (years)	**n=5289**
Median (25th, 75th)	14 (5, 30)
Mean (SD)	20 (18)
Min, Max	<0‡, 91
Age at Diagnosis†, n (%)	**n=5289**
Prenatal‡ to <10 years	2252 (43)
10 to <20 years	877 (17)
20 to <30 years	807 (15)
30 to <40 years	550 (10)
40 to <50 years	380 (7)
50 to <60 years	224 (4)
60 to <70 years	135 (3)
70 years or more	64 (1)
Treatment Status, n (%)	**n=5704**
Ever on imiglucerase	4514 (79)
Never on imiglucerase	1190 (21)
Age at First Infusion, (years)	**n=4495**
Median (25th, 75th)	26 (9, 42)
Mean (SD)	27 (20)
Min, Max	0, 87
Age at Last Follow-up, (years)	**n=5710**
Median (25th, 75th)	33 (17, 51)
Mean (SD)	35 (21)
Min, Max	<0‡, 92

Data from Gaucher Registry 2010

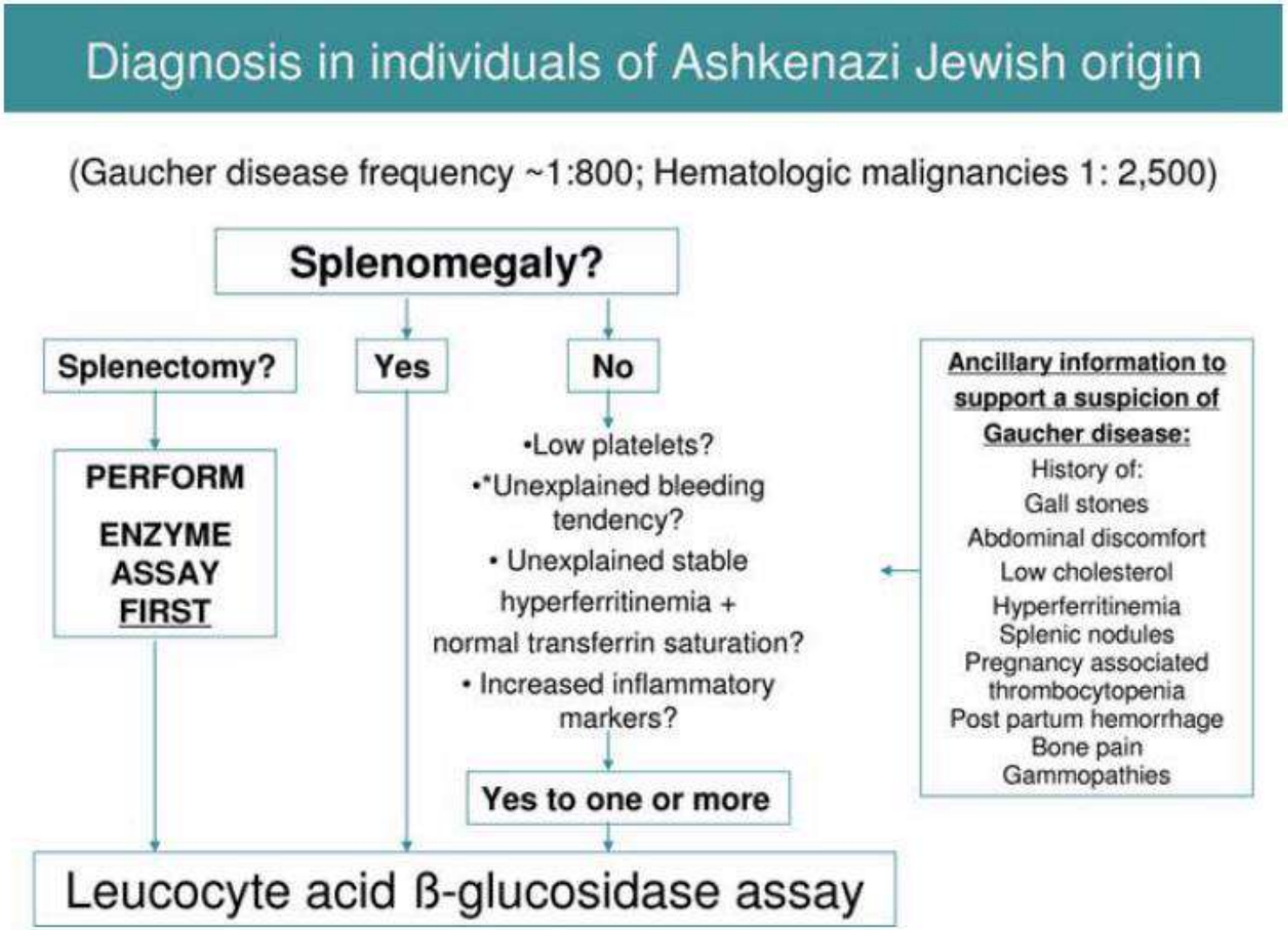
Algoritmo Diagnostico



*In patients with bleeding diatheses, coagulopathies such as factor XI deficiency common in Askenazim [34] should be excluded.

Mistry et al., Am J Hematol, 2011; 86(1): 110-115

Algoritmo Diagnostico

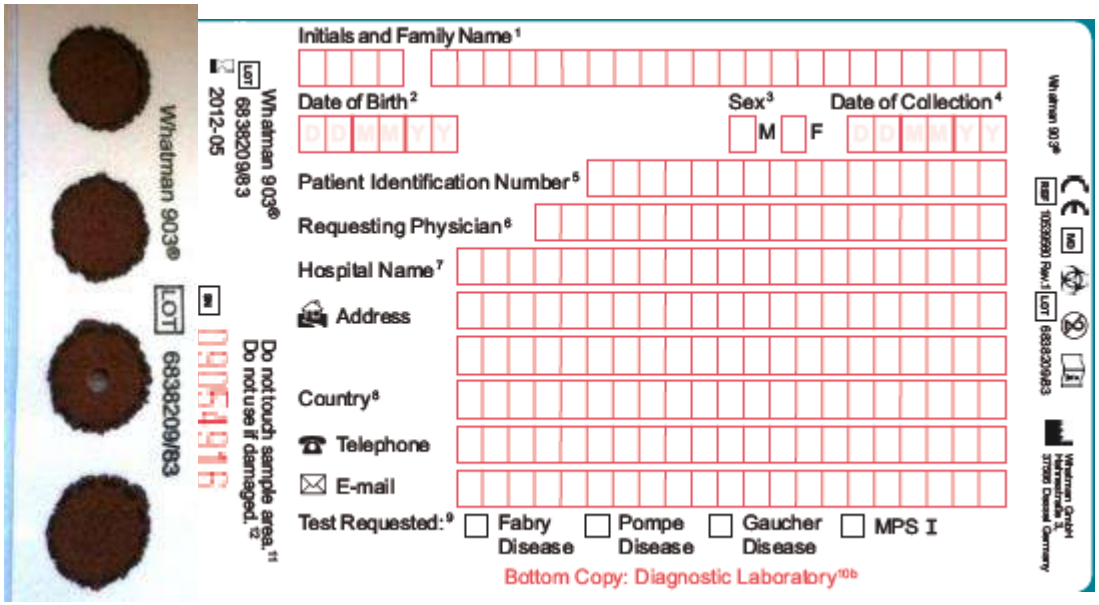


*In patients with bleeding diatheses, coagulopathies such as factor XI deficiency common in Askenazim [34] should be excluded.

Mistry et al., Am J Hematol, 2011; 86(1): 110-115

CONFERMA DIAGNOSTICA

DBS: dry blood spot, dosaggio enzimatico



Analisi molecolare

Stroppiano M, 2014, Clin Biochem, 47: 1293-1296.

Complicanze nell'adulto

COLELITIASI

TUMORI SOLIDI

Carcinoma epatocellulare
Melanoma

MALATTIE EMATOLOGICHE
(rischio 14.7 volte)

- mieloma multiplo (rischio: 5.9 volte)
- MGUS
- linfomi/leucemie

Taddei TH et al. J Inherit Metab Dis 2010; 33(3):291-300;
Rosenbloom et al. Blood 2005;105:4569-4572;
de Fost M et al. Blood Cells Mol Dis 2006; 36: 53-58;
Hughes D et al. Br J Haematol 2007; 138: 676-86.

Complicanze nell'adulto

PARKINSONISMO

- rischio elevato di pazienti con GD di sviluppare M. Parkinson

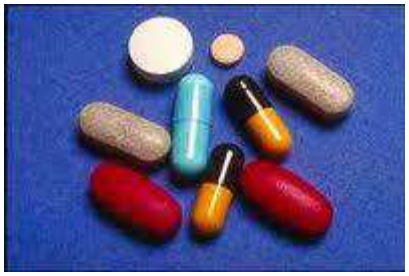
- soggetti portatori di una mutazione per GD ad aumentato rischio per M. Parkinson (giovanile e con deficit cognitivo)

- sesso maschile e aumento dell'età in pz GD sembrano fattori di rischio (Chetrit et al.)

Bultron G et al. J Inherit Metab Dis 2010; 33(2): 167-73;
Chetrit EB et al. Blood Cells Mol Dis 2013; 50(3): 218-21.

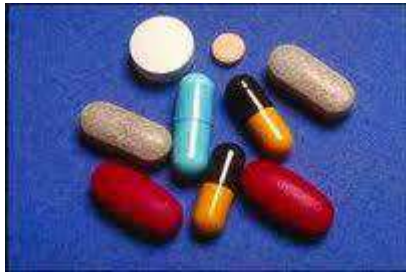
TERAPIE DISPONIBILI

TERAPIA ENZIMATICA SOSTITUTIVA (ERT)



TERAPIA CON INIBITORI DEL SUBSTRATO (SRT)

TERAPIA DI SUPPORTO



SRT

Lancet. 2015 Jun 13;385(9985):2355-62. doi: 10.1016/S0140-6736(14)61841-9. Epub 2015 Mar 26.

Eliglustat compared with imiglucerase in patients with Gaucher's disease type 1 stabilised on enzyme replacement therapy: a phase 3, randomised, open-label, non-inferiority trial.

Cox TM[1], Drelichman G[2], Cravo R[3], Balwani M[4], Burrow TA[5], Martins AM[6], Lukina E[7], Rosenbloom B[8], Ross L[9], Angell J[9], Puga AC[9].

INTERPRETATION: Oral eliglustat maintained haematological and organ volume stability in adults with Gaucher's disease type 1 already controlled by intravenous ERT and could be a useful therapeutic option.

IN FASE DI REGISTRAZIONE

TERAPIA DI SUPPORTO

- **Calcio, vitamina D e difosfonati**

- **Terapia delle singole complicanze**

APPROCCIO TERAPEUTICO

ELSEVIER

Seminars in HEMATOLOGY

Gaucher Disease Type 1: Revised Recommendations on Evaluations and Monitoring for Adult Patients

Neal J. Weinreb,[a] Mario C. Aggio,[b] Hans C. Andersson,[c] Generoso Andria,[d] Joel Charrow,[e] Joe T.R. Clarke,[f] Anders Erikson,[g] Pilar Giraldo,[h] Jack Goldblatt,[i] Carla Hollak,[j] Hiroyuki Ida,[k] Paige Kaplan,[l] Edwin H. Kolodny,[m] Pramod Mistry,[n] Gregory M. Pastores,[m] Ricardo Pires,[o] Ainu Prakesh-Cheng,[p] Barry E. Rosenbloom,[q] C. Ronald Scott,[r] Elisa Sobreira,[s] Anna Tylki-Szymańska,[t] Ashok Vellodi,[u] Stephan vom Dahl,[v] Rebecca S. Wappner,[w] and Ari Zimran[x]

Stadiazione di patologia

Terapia e follow-up

ELSEVIER

Seminars in HEMATOLOGY

Therapeutic Goals in the Treatment of Gaucher Disease

Gregory M. Pastores,[a] Neal J. Weinreb,[b] Hans Aerts,[c] Generoso Andria,[d] Timothy M. Cox,[e] Manuel Giralt,[f] Gregory A. Grabowski,[g] Pramod K. Mistry,[h] and Anna Tylki-Szymańska[i]

Pastores GM, et al. *Semin Hematol*. 2004;41(4 suppl 5):4-14.

Ringraziamenti

Giovanna Fabio
Cinzia Hu
Francesca Minonzio
Laura Zanaboni
Giovanna Graziadei
Elena Cassinerio
Marina Baldini
Adriana Branchi

Michela

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