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Diagnostic Algorithms in Suspected Gaucher Disease

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Disclosure Statement

I am Associate Professor of the Ribeirão Preto Medical School, University of São Paulo, full time, and I have no conflicts of interest

Advisor / Coordinator of the International Collaborative Gaucher Group – Gaucher Registry (ICGG – GR)

Supported pela Genzyme / Sanofi

Brazil / Latin America / Member of the Global Board

I have received educational grants for conferences and travel

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Gaucher Disease (GD), 1882: Female patient, 23 Years old, primitive spleen epithelioma?

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

Avec figures dans le texte.

Président..... M. BOUCHARD, professeur.

Suffragants..... MM. { JACCOUD, professeur. / RICHELOT, agrégé / RATHERY, agrégé

Le candidat répondra aux questions qui lui seront posées sur les diverses parties de l'enseignement médical.

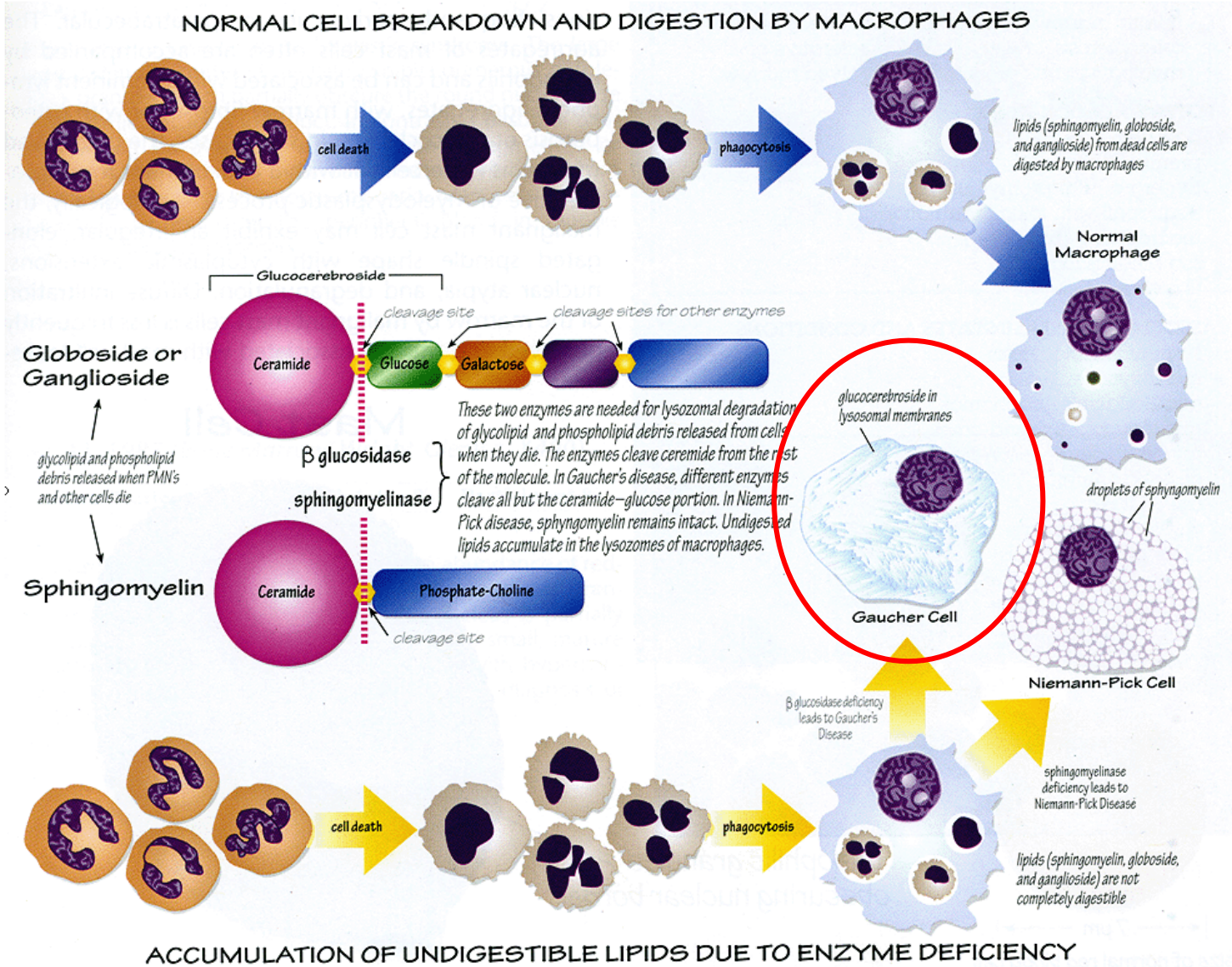
PARIS

OCTAVE DOIN, ÉDITEUR

8, PLACE DE L'ODÉON, 8

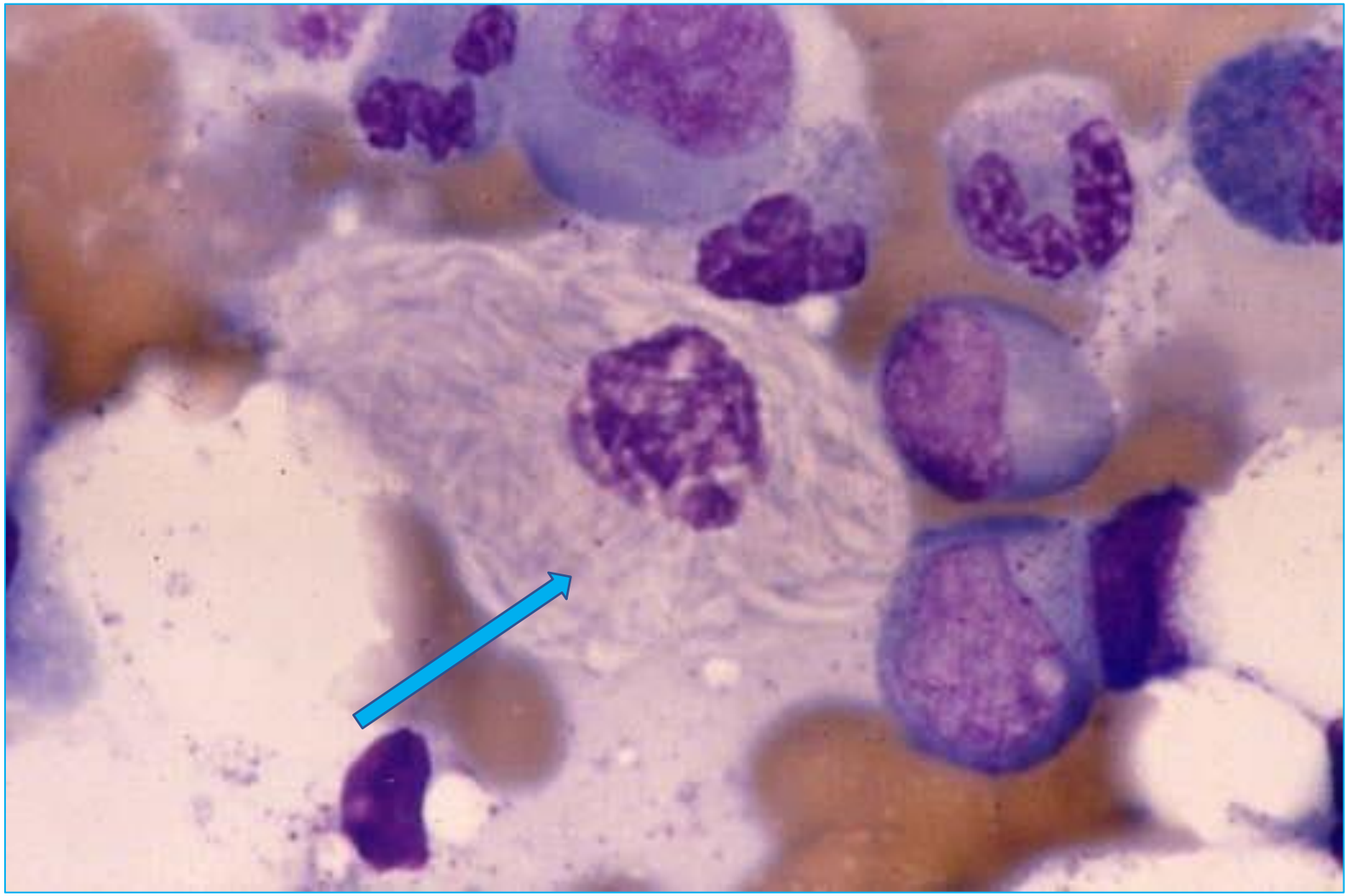
1882

Lysosomal accumulation of sphingolipids



Color Atlas of Hematology 1998: 327.

Gaucher Cells



(Sidransky E. Molecular Genetics and Metabolism 2004; 83: 6-15)

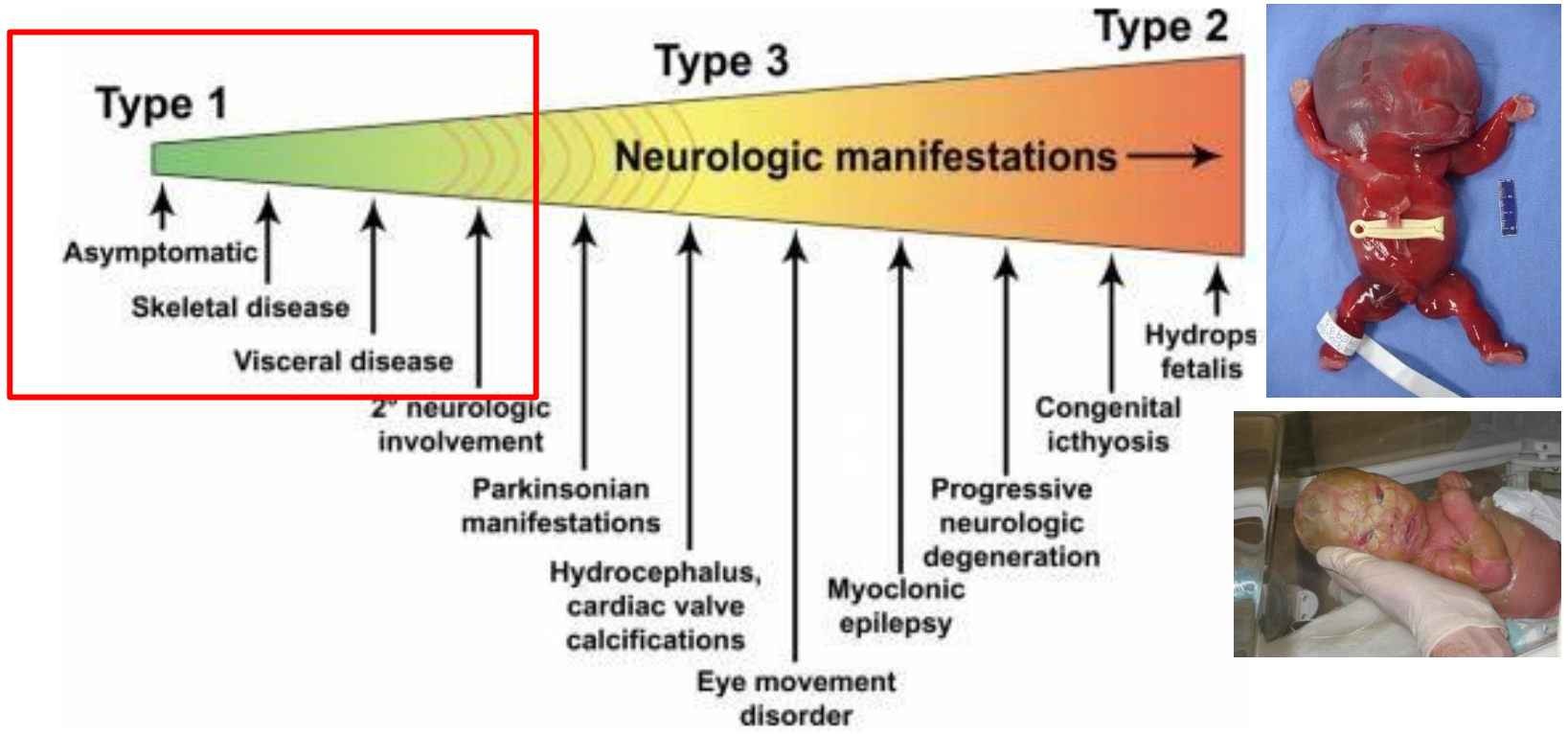


Fig. 1. Gaucher disease presents with a wide spectrum of phenotypes with the primary distinction being the presence or absence of neurologic manifestations. There is a "grey zone," indicated by curved lines, where it is not clear if the neuropathology is the result of the enzyme deficiency or of a secondary cause.

Gaucher disease types 1 and 3: Phenotypic characterization of large populations from the ICGG Gaucher Registry

Gregory A. Grabowski,[1]* Ari Zimran,[2] and Hiroyuki Ida[3]

S12 American Journal of Hematology, Vol. 90, No. S1, July 2015

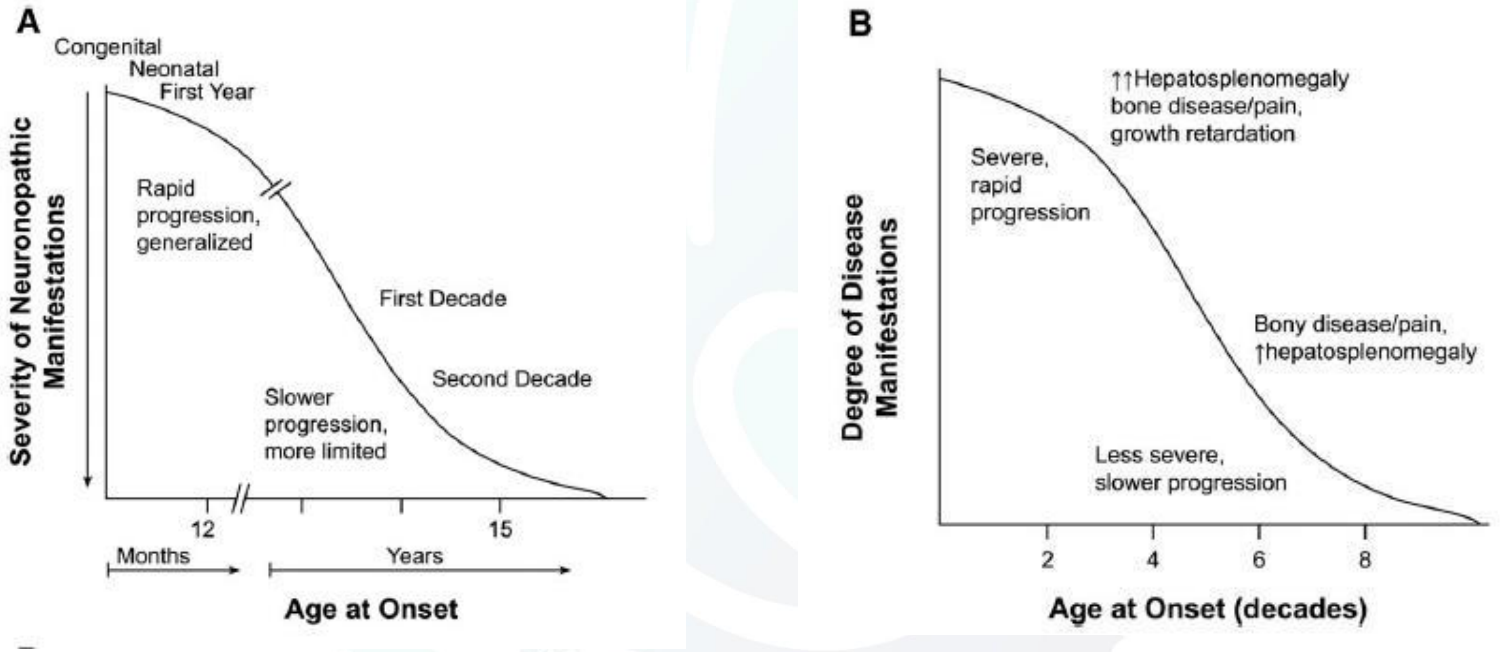


Figure 1. Schematics of the continuum of phenotypes in the neuronopathic (A) and nonneuronopathic (B) Gaucher disease variants. In (A) the degree and progression of the neuronopathic manifestations are summarized for the several variants, types 2 and 3, that present with primary CNS disease. In (B) the variation in the visceral manifestations of the type 1 variants that do not manifest primary, early-onset CNS disease. Adapted from Ref. 5 with permission from McGraw-Hill.

Diagnostic Drivers:

Hepatosplenomegaly

Splenomegaly & Thrombocytopenia

scientific reports

Check for updates

OPEN

Predicting the probability of Gaucher disease in subjects with splenomegaly and thrombocytopenia

Irene Motta[1,2], Dario Consonni[3], Marina Stroppiano[4], Christian Benedetto[5], Elena Cassinerio[1], Barbara Tappino[4], Paola Ranalli[6], Lorenza Borin[7], Luca Facchini[8], Andrea Patriarca[9], Wilma Barcellini[10], Federica Lanza[4], Mirella Filocamo[4], Maria Domenica Cappellini[1,2]✉ & Splenomegaly Gaucher group*

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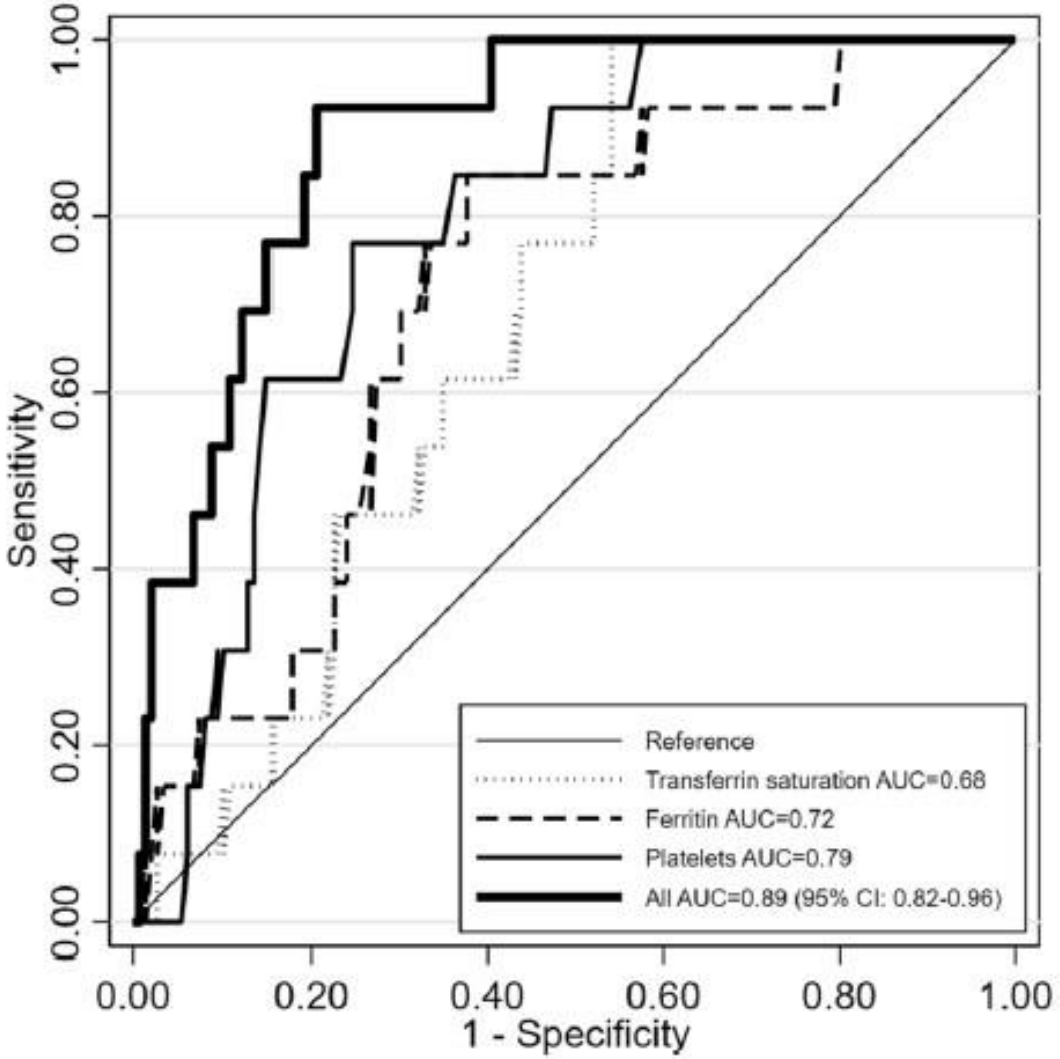
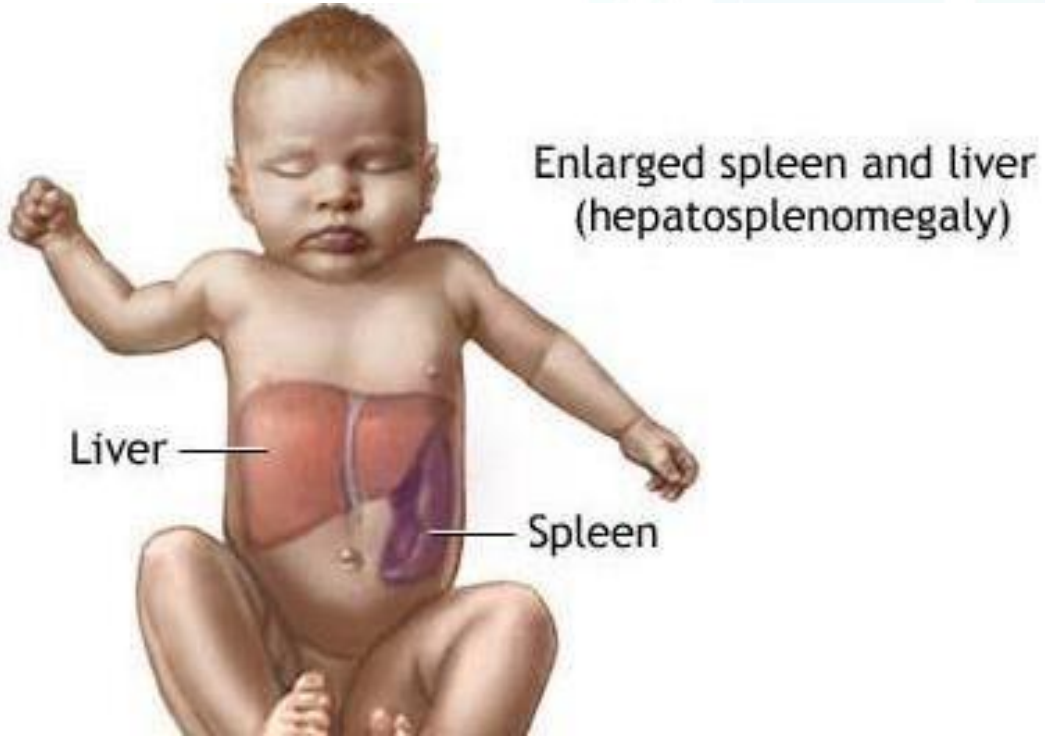


Figure 2. Receiver operating characteristic (ROC) curves of GD1 for platelets (thousands/mm^3), ferritin (μg/L), transferrin saturation (%), and for the three variables jointly analyzed in a multiple logistic regression model. *AUC* area under the curve, *CI* confidence interval.

Hepatosplenomegaly

- Increase of the liver and spleen size above the expected values for the age



- Normal values of the liver & spleen according to the age:
  1. Liver – 3 cm under the right rib cage for newborn; 5 cm of hepatimetry in the week of life; 7-8 cm for boys and 6,5 cm for girls;
  2. Spleen is palpable at 1-2 cm LRC in 50% of the neonates, 10% of the infants and 5% of the healthy adolescents

Hepatosplenomegaly – Etiopathogenesis

- There are 5 general mechanisms :

1. Inflammation
2. Cellular Infiltration
3. Blood Flow Congestion
4. Biliary Obstruction
5. Over-Deposit – Storage Disorders

Hepatosplenomegaly – Inflammatory Mechanism

- Infections caused by:
  - Virus (A, B, C hepatites, CMV, Epstein-Barr)
  - Bacteria (kala azar, brucellosis, etc), fungii and parasites

- This mechanism is also seen in situations such as:
  - Toxic
  - Radiations
  - Auto imune diseases

Hepatosplenomegaly – Cellular Infiltration

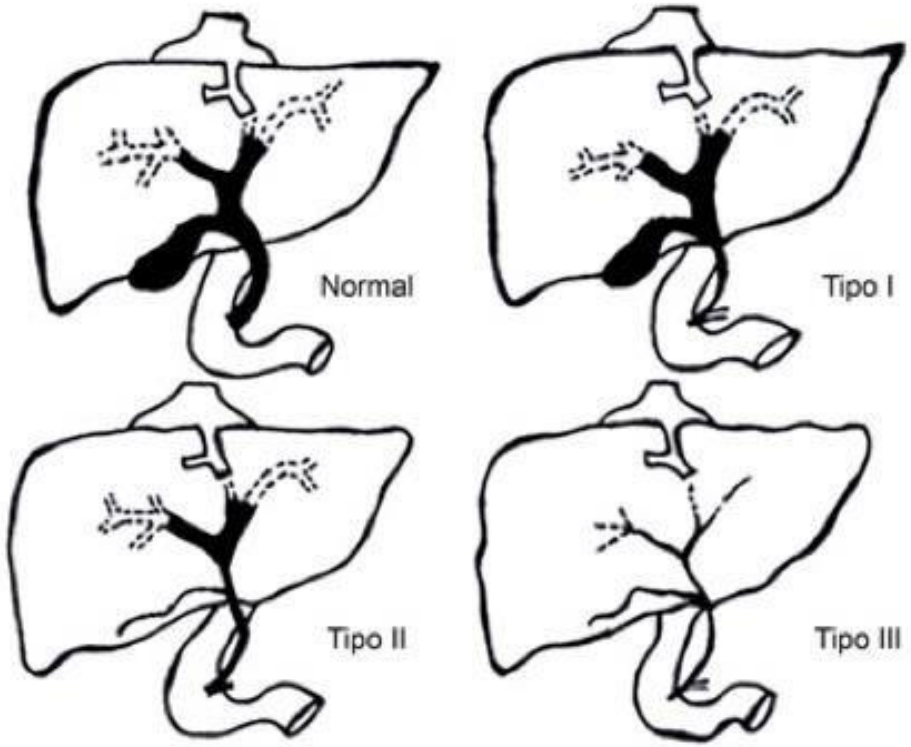
- Cellular infiiltration is the accumulation of tissue cells or those cells that migrate from tissues distant from liver and spleen:

1. Liver:
   - hepatoblastoma, hepatocarcinoma, hemangiomas, parasitic cysts

2. Extrahepatic:
   - Leukemias, Wilms tumor

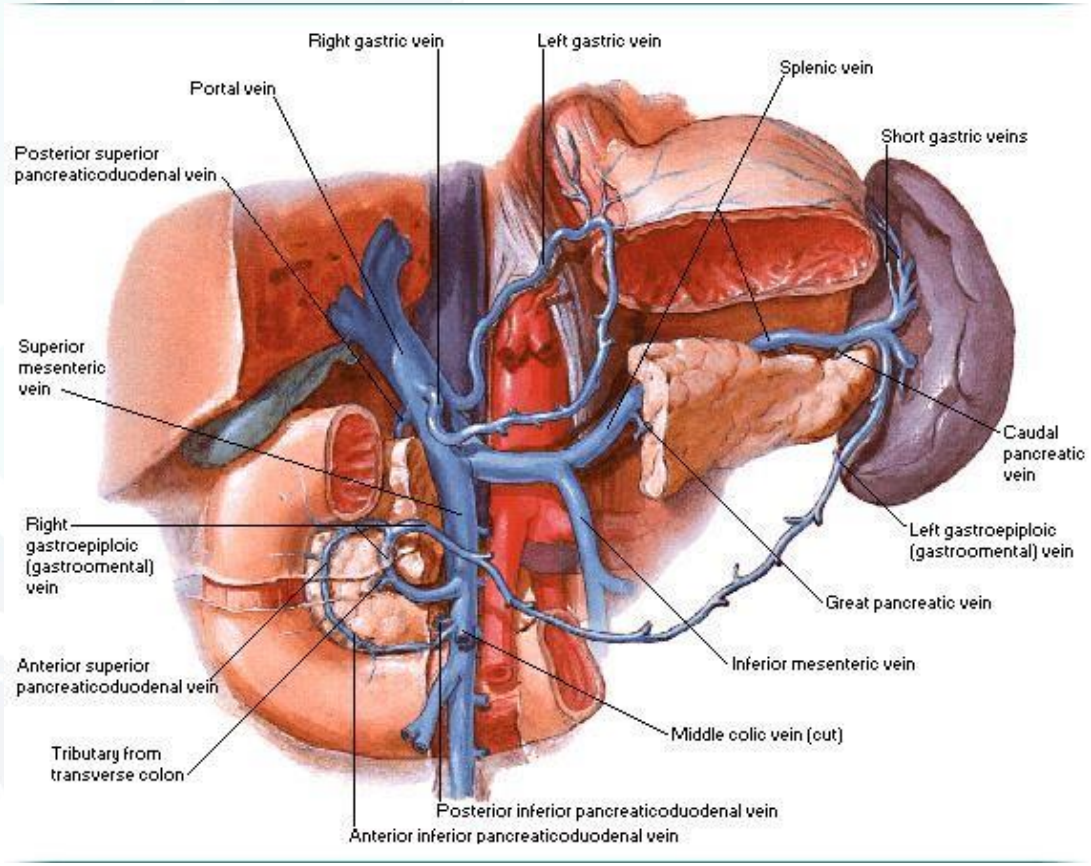
Hepatosplenomegaly – Biliary Obstruction

- Produce alterations by cholestasis
- Intrahepatic
  - Biliary atresia
  - Extrahepatic
  - Cystic fibrosis
- Extrahepatic
  - Biliary lithiasis
  - Choledocal cysts
  - Biliary atresia



Hepatosplenomegaly – Blood Flow Congestion

- Portal Hypertension with hypersplenism:
  - Excessive spleen function with erytrhocytes, leukocytes and platelets hyjacking, leading to a mild or moderate decrease of these cellular lineages in circulation
  - Schistosomiasis, for example



Hepatosplenomegaly – Storage Disorders

- It can occur by accumulation of:

1. Proteins:
   - Deficiency of alpha-1-antitrypsin
2. Metals – Cupper:
   - Wilson´s disease

1. <u>Macromolecules – IEM</u>:
   1. Glucose polymers:
      - GSDs
   2. Glycosaminoglycans:
      - Mucopolysaccharidoses
   3. Lipids:
      - Lysosomal Acid Lipase Deficiency (LAL-D)
      - Niemann-Pick A, B, C
      - **Gaucher Disease**

Diagnostic Drivers:

Skeleton / Bone Disease

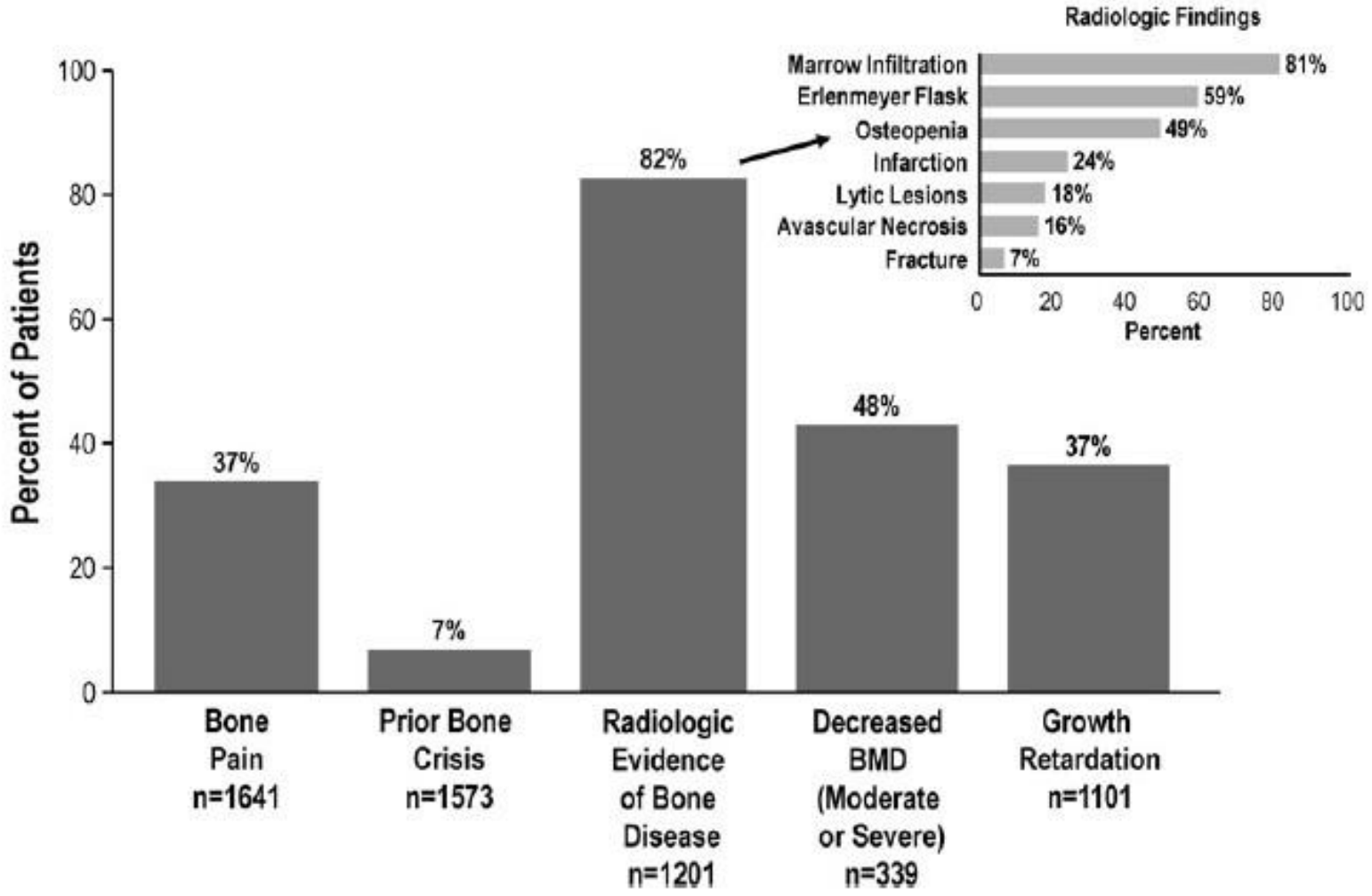
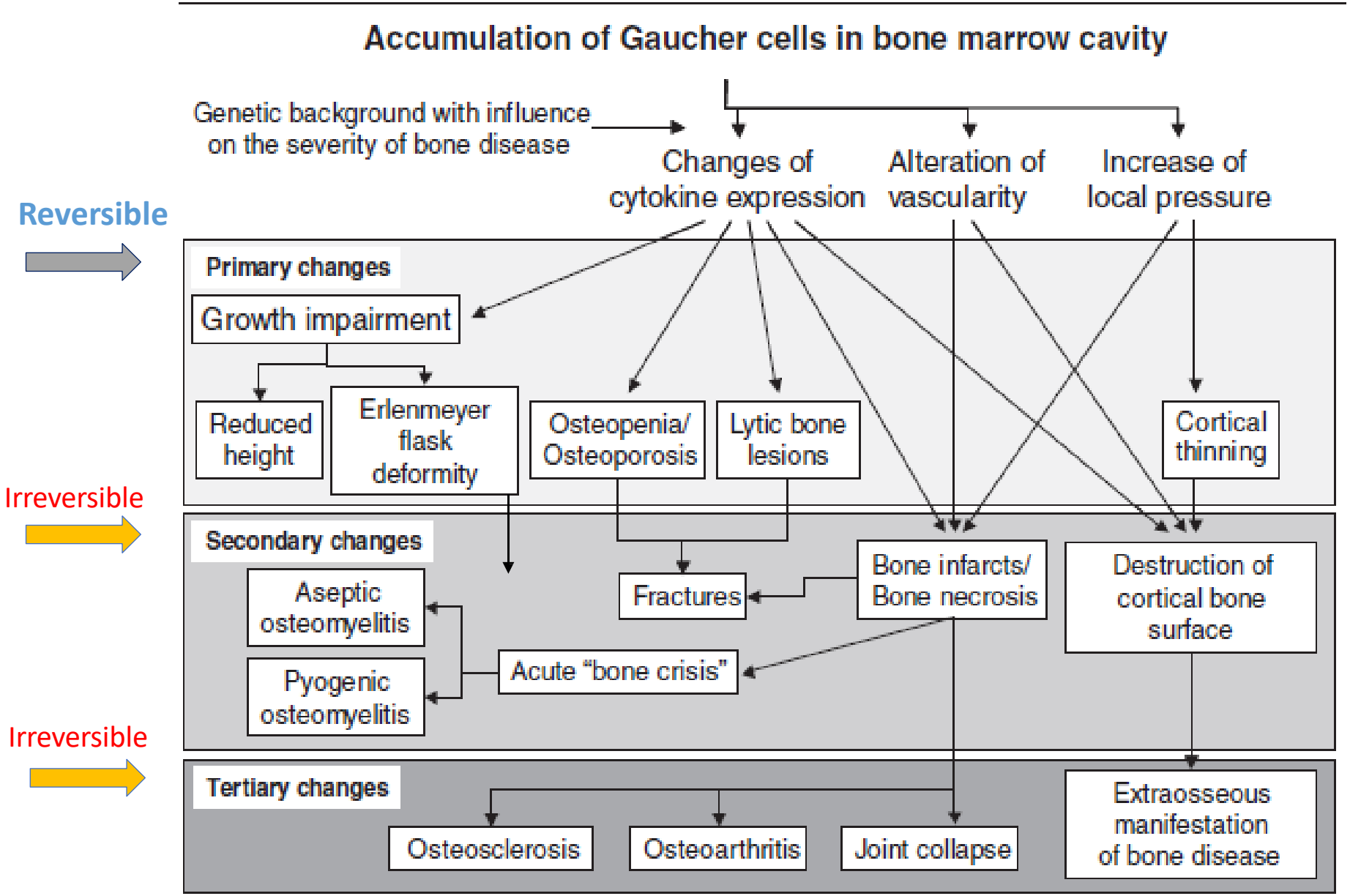


Fig. 1. Baseline bone manifestations in patients with type 1 Gaucher disease before therapy (Gaucher Registry Annual Report 2010).

Goker-Alpan O. Molecular Genetics and Metabolism 104 (2011) 438–447



Mikosch P & Hughes D. Wien Med Wochernschr 2010;160(23):609-624

Artigo Original/Artículo Original/Original Article

GAUCHER DISEASE TYPE 1 IN THE SKELETON: REVIEW OF LATIN AMERICA

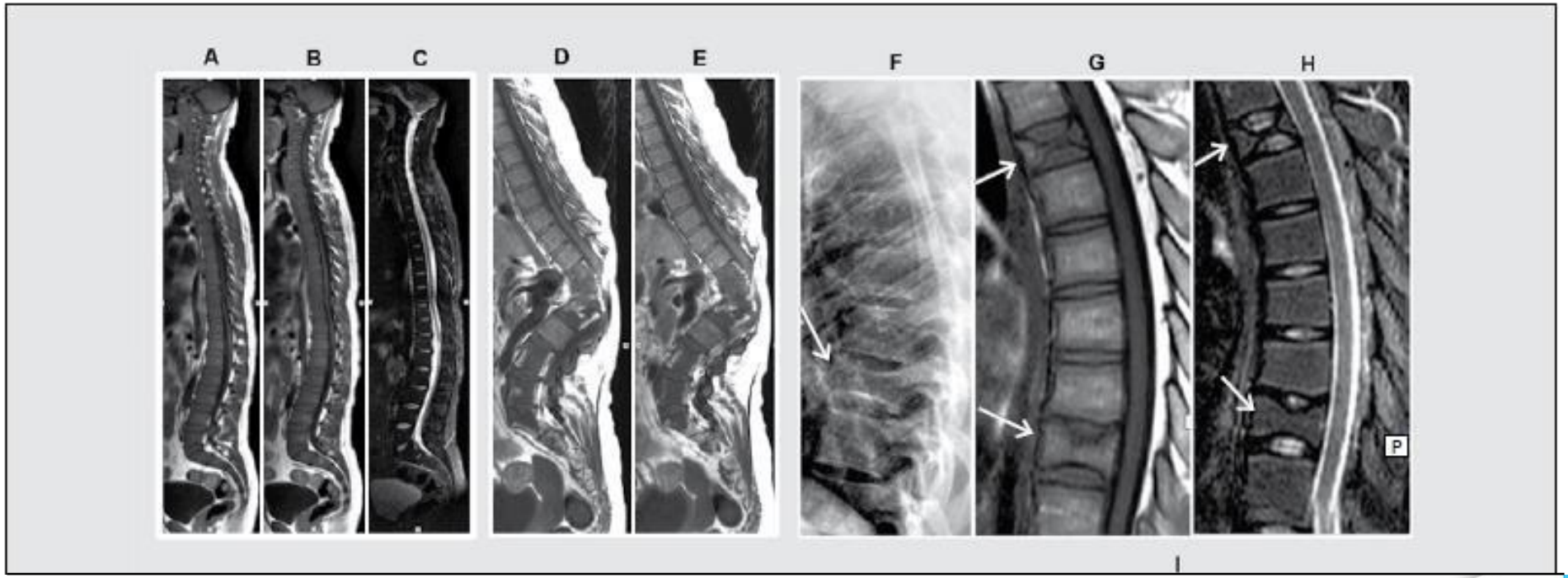
DOENÇA DE GAUCHER TIPO 1 NO ESQUELETO: REVISÃO DA AMÉRICA LATINA

ENFERMEDAD DE GAUCHER TIPO 1 EN EL ESQUELETO: REVISIÓN DE AMÉRICA LATINA

José Simon Camelo Júnior[1], Marta Dragosky[2], Guillermo Drelichman[3]

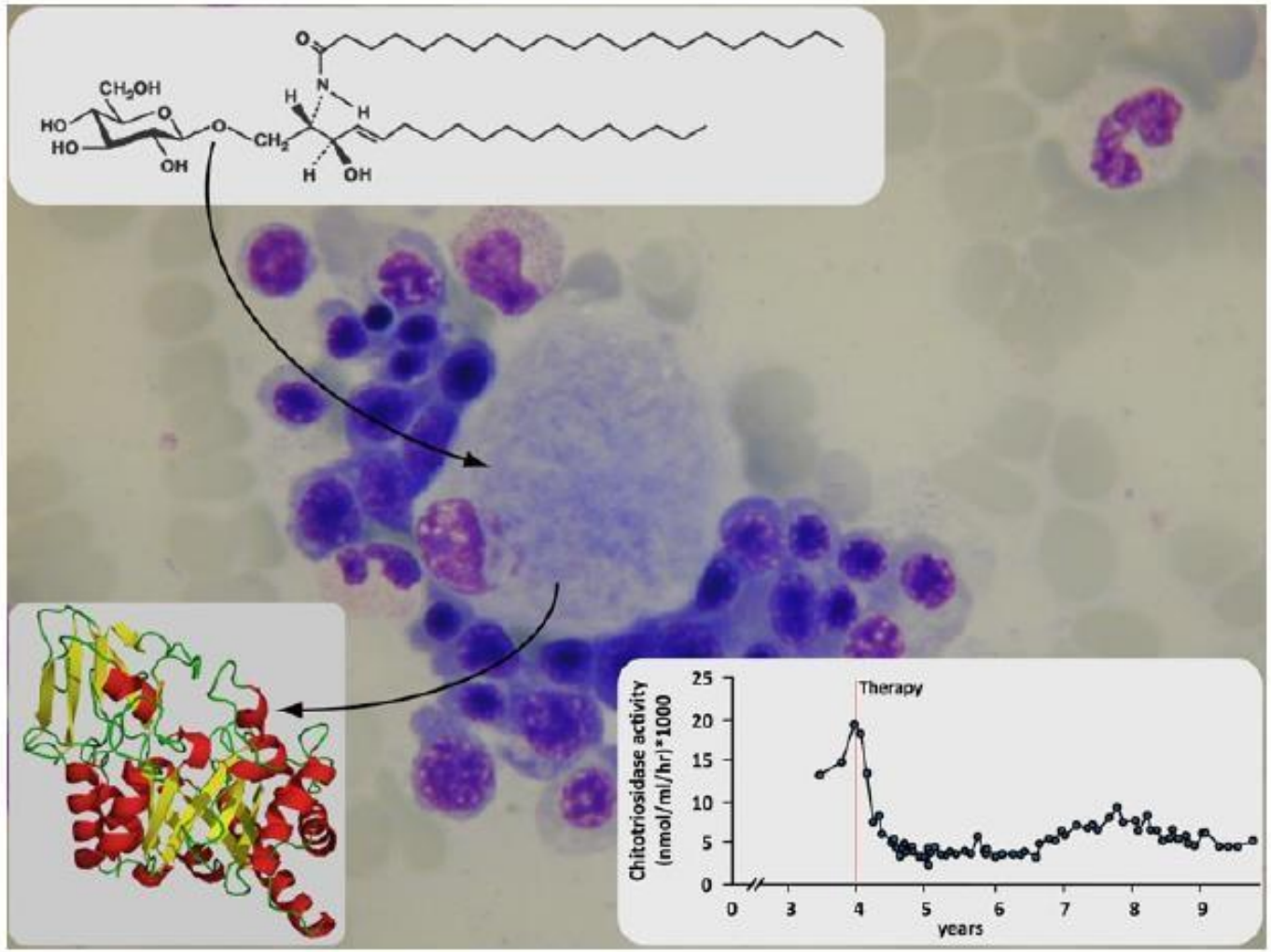
1. Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Departamento de Pediatria, Ribeirão Preto, SP, Brasil.
2 - Henry Moore Institute, Buenos Aires, Argentina.
3 - R. Gutiérrez Children's Hospital, Buenos Aires, Argentina.

Coluna Columna 2016; 15(4), 317-24
http://dx.doi.org/10.1590/S1808-185120161504166050



Biomarkers: Chitotriosidase

Fig. 1 Gaucher cell accumulating the glycosphingolipid glucosylceramide and specifically secreting the biomarker chitotriosidase that can be detected in plasma. Example of corrections in plasma chitotriosidase in Gaucher disease patients receiving enzyme replacement therapy



Chitotriosidase Deficient Patients

- Interpretation of the Chitotriosidase levels is complicated by the occurrence of a duplication of 24 pairs of bases on gene CHIT1, truncating the production of the protein.
- In most of the ethnic groups, 1:3 of the individuals carry onthis abnormality and 1:20 of the individuals are homozygous:
  - DEFICIENCY OF CHITOTRIOSIDASE
- Levels of plasmatic PARC/ CCL18 (pulmonary and activation-regulated chemokine) are 10-40-fold more elevated in symptomatic patients with GD; elevated measurements of plasmatic PARC/CCL18 represents a good toolto monitor the burden of Gaucher cells in patients CHITO-deficient.

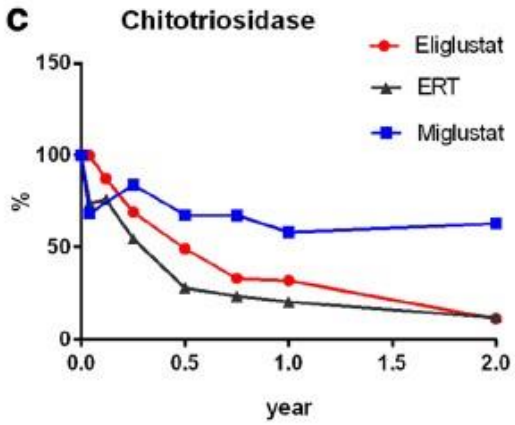
Other Biomarkers: Lyso-GL1

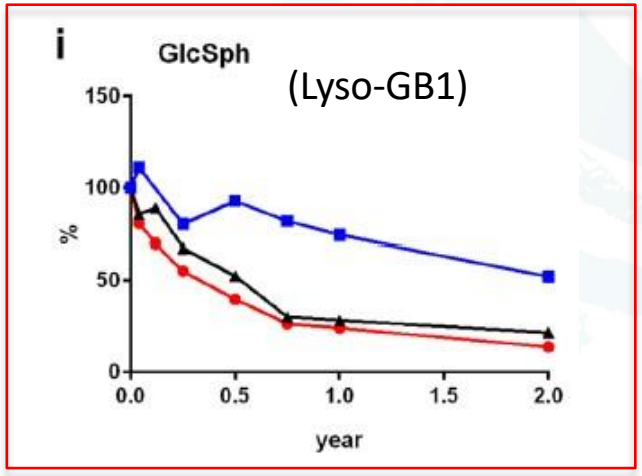
RESEARCH Open Access

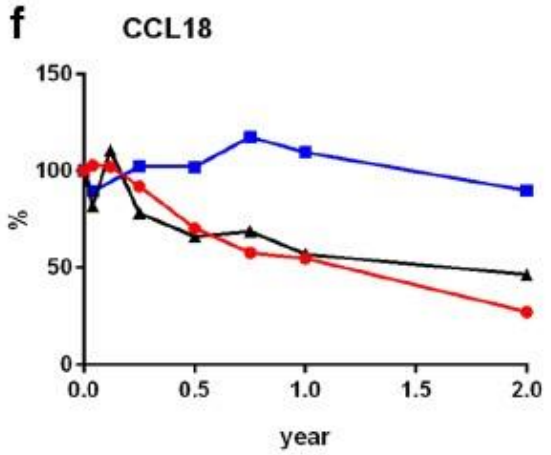
Biochemical response to substrate reduction therapy versus enzyme replacement therapy in Gaucher disease type 1 patients

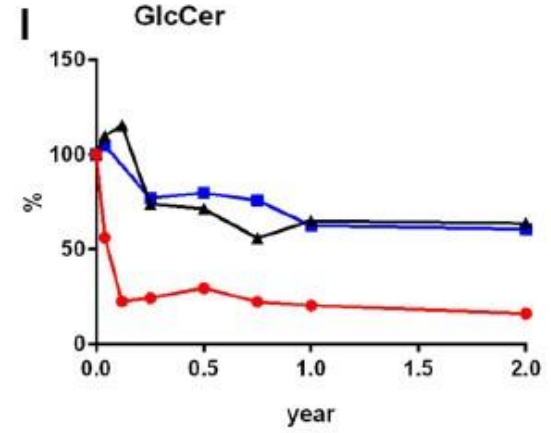
Bouwien E. Smid[1†], Maria J. Ferraz[2†], Marri Verhoek[3], Mina Mirzaian[2], Patrick Wisse[4], Herman S. Overkleeft[4], Carla E. Hollak[1] and Johannes M. Aerts[3,5*]

Smid *et al. Orphanet Journal of Rare Diseases* (2016) 11:28
DOI 10.1186/s13023-016-0413-3









NÄIVE PATIENTS

Diagnostic Scores

INTERNAL MEDICINE JOURNAL

RACP Specialists. Together

doi:10.1111/imj.14942

Scoring system to facilitate diagnosis of Gaucher disease

Atul Mehta,[1] Oliver Rivero-Arias,[2] Magy Abdelwahab,[3] Samantha Campbell,[4] Annabel McMillan,[5] Mark J. Rolfe,[6] Jeremy R. Bright[6] and David J. Kuter[7,8]

[1]Department of Haematology, University College London, and Departments of [4]Hepatology and Gastroenterology, Royal Free Hospital, and [5]Haematology, Royal Free Hospital, University College London School of Medicine, London, and [2]Nuffield Department of Population Health, National Perinatal Epidemiology Unit, University of Oxford, and [6]Oxford PharmaGenesis, Oxford, UK, [3]Department of Paediatric Haematology, Cairo University Paediatric Hospital, Cairo, Egypt, and [7]Department of Medicine, Harvard Medical School, and [8]Center for Hematology, Massachusetts General Hospital, Boston, Massachusetts, USA

Table 1 Prototype point-scoring system for diagnostic testing in Gaucher disease (GD), based on factors identified as potentially indicative of type 1 GD (adapted from Mehta *et al.*)[9]

	Weighting	Clinical sign or covariable
Major signs and covariables	3 points	Splenomegaly (≥3 × normal)
	2 points	Thrombocytopenia, mild or moderate (platelet count, 50–140 × 10^9/L)
		Bone issues, including pain, crises, avascular necrosis and fractures
		Family history of GD
		Anaemia, mild or moderate (haemoglobin, F ≥90–130 g/dL; M ≥90–140 g/dL)
		Hyperferritinaemia, mild or moderate (serum ferritin, 300–1000 µg/L)
		Jewish ancestry
		Hepatomegaly, mild or moderate (≤3 × normal)
		Gammopathy, monoclonal or polyclonal
	1 point	Anaemia, severe (haemoglobin, <90 g/dL)
		Hyperferritinaemia, severe (serum ferritin, >1000 µg/L)
		Hepatomegaly, severe (>3 × normal)
		Thrombocytopenia, severe (platelet count, <50 × 10^9/L)
Minor signs and covariables	0.5 points†	Bleeding, bruising or coagulopathy
		Leukopenia

Mehta *et al.*

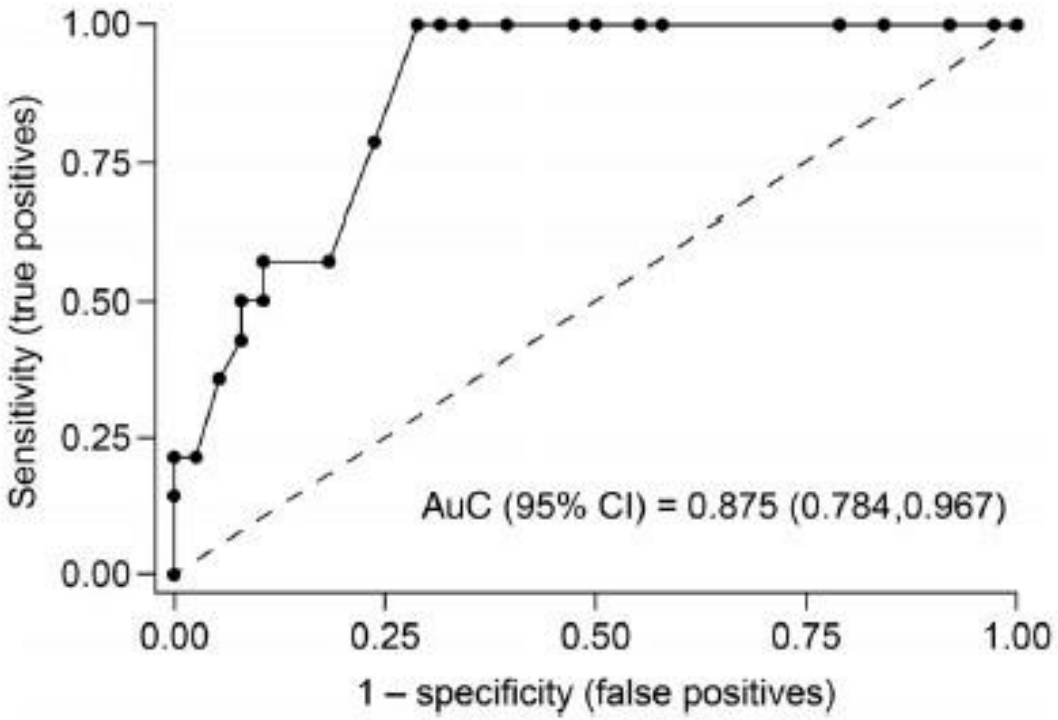


Figure 1 The receiver-operating characteristic (ROC) curve illustrating the accuracy† of the prototype point-scoring system (11 factors) for identifying Gaucher disease in the sample population (*n*/*N* = 52/100). †The closer the area under the ROC curve is to 1, the more accurate the diagnostic tool. *n*, number of patient records included in the analysis; *N*, sample population. AuC, area under the curve; CI, confidence interval.

Diagnostic Drivers:

Algorithms

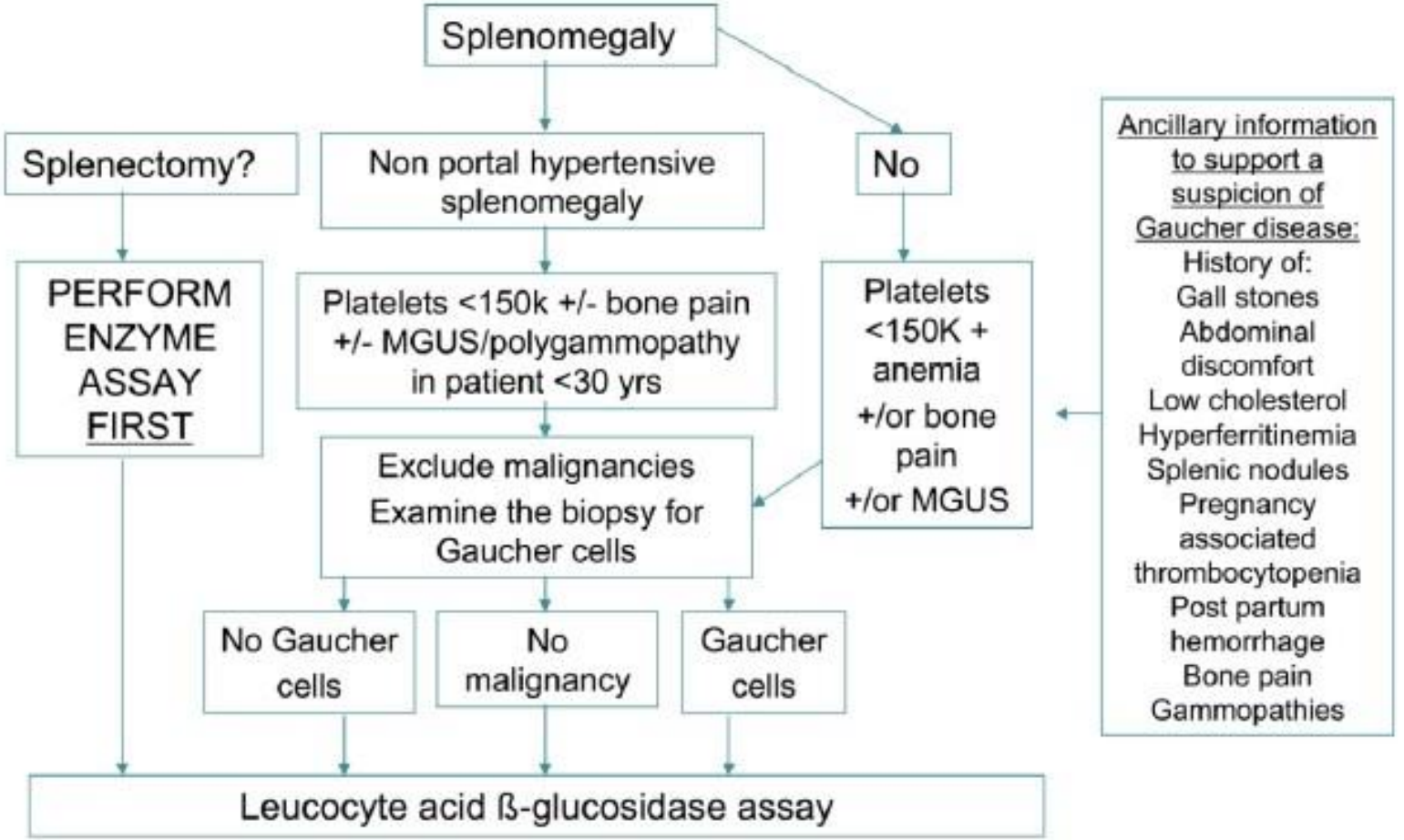
Published in final edited form as:
Am J Hematol. 2011 January ; 86(1): 110–115. doi:10.1002/ajh.21888.

Consensus Conference: A reappraisal of Gaucher disease - diagnosis and disease management algorithms

Pramod K. Mistry[1,*], **Maria Domenica Cappellini**[2], **Elena Lukina**[3], **Hayri Özsan**[4], **Sara Mach Pascual**[5], **Hanna Rosenbaum**[6], **Maria Helena Solano**[7], **Zachary Spigelman**[8], **Jesús Villarrubia**[9], **Nora Patricia Watman**[10], and **Gero Massenkeil**[11]

Diagnosis in individuals of non-Ashkenazi Jewish origin

Gaucher disease ~1: 40,000-100,000: Hematologic malignancies ~40:100,000



Pediatr Blood Cancer 2014;61:1905–1909

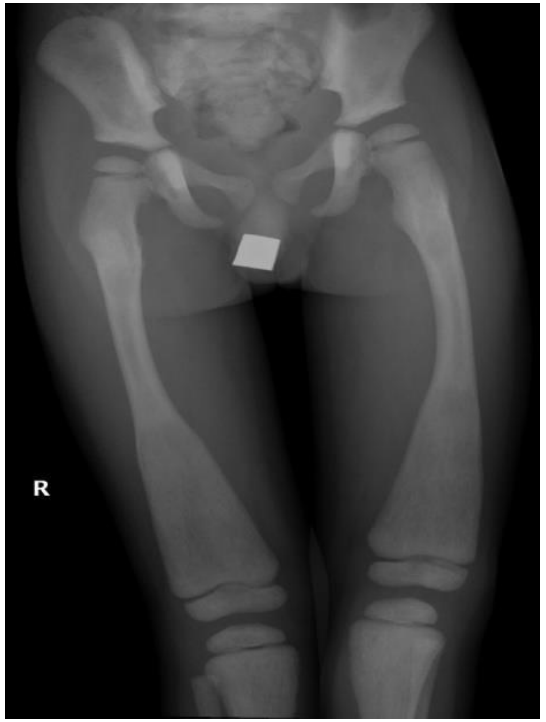
REVIEW

Early Diagnosis of Gaucher Disease in Pediatric Patients: Proposal for a Diagnostic Algorithm

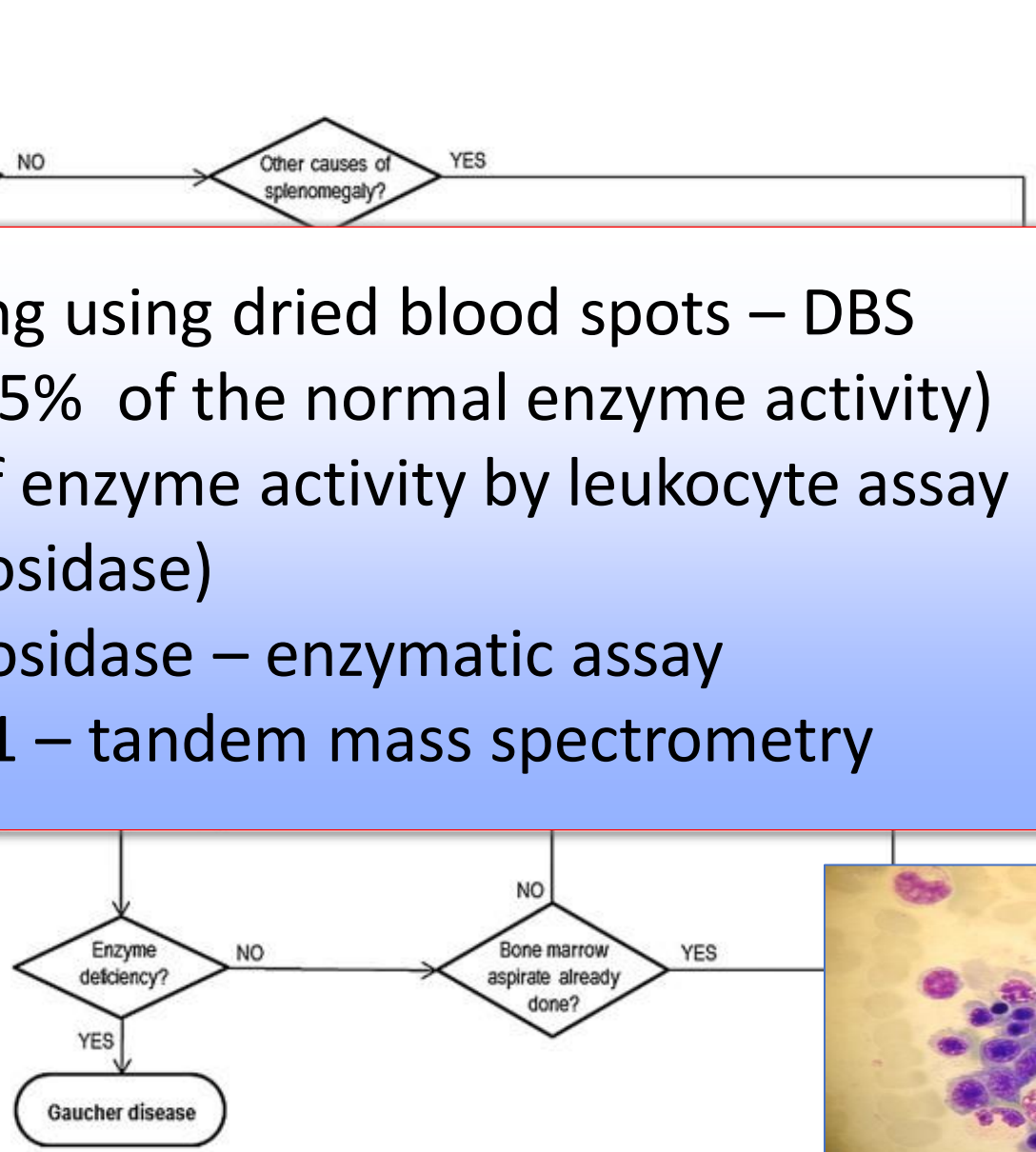
Maja Di Rocco, MD,[1]* Generoso Andria, MD,[2] Federica Deodato, MD,[3] Fiorina Giona, MD,[4] Concetta Micalizzi, MD,[5] and Andrea Pession, MD[6]

Gaucher disease (GD) is caused by an enzyme deficiency that leads to the accumulation of glycolipids in various organs. Although the signs and symptoms of GD emerge in childhood in the majority of patients, the disease often remains unrecognized for many years with delay of benefits of therapy or development of irreversible complications. Based on published data and data from the International Collaborative Gaucher Group Registry, an algorithm has been drafted for early diagnosis of GD in pediatric patients. It will help hematologists in promoting a timely diagnosis and early access to therapy for pediatric patients with GD. Pediatr Blood Cancer 2014;61:1905–1909.

Key words: algorithm; Gaucher disease; pediatric age



- Screening using dried blood spots – DBS
  (5-25% of the normal enzyme activity)
- Level of enzyme activity by leukocyte assay (β-glucosidase)
- Chitotriosidase – enzymatic assay
- Lyso-GL1 – tandem mass spectrometry



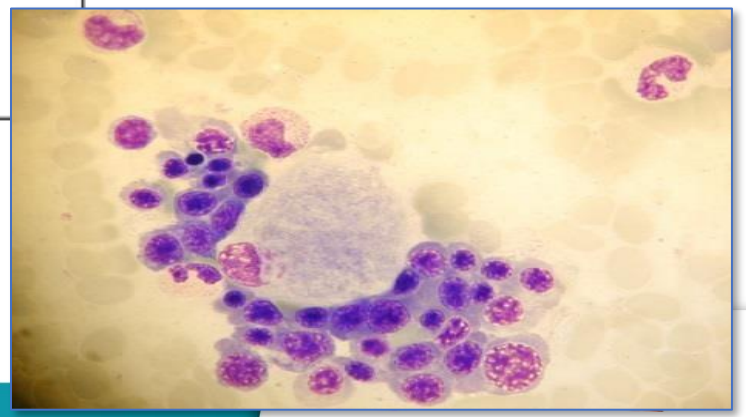


Fig. 1. A proposed algorithm for early diagnosis of GD in the pediatric age group.

ARTÍCULO ORIGINAL

MEDICINA (Buenos Aires) 2020; 80: 487-494

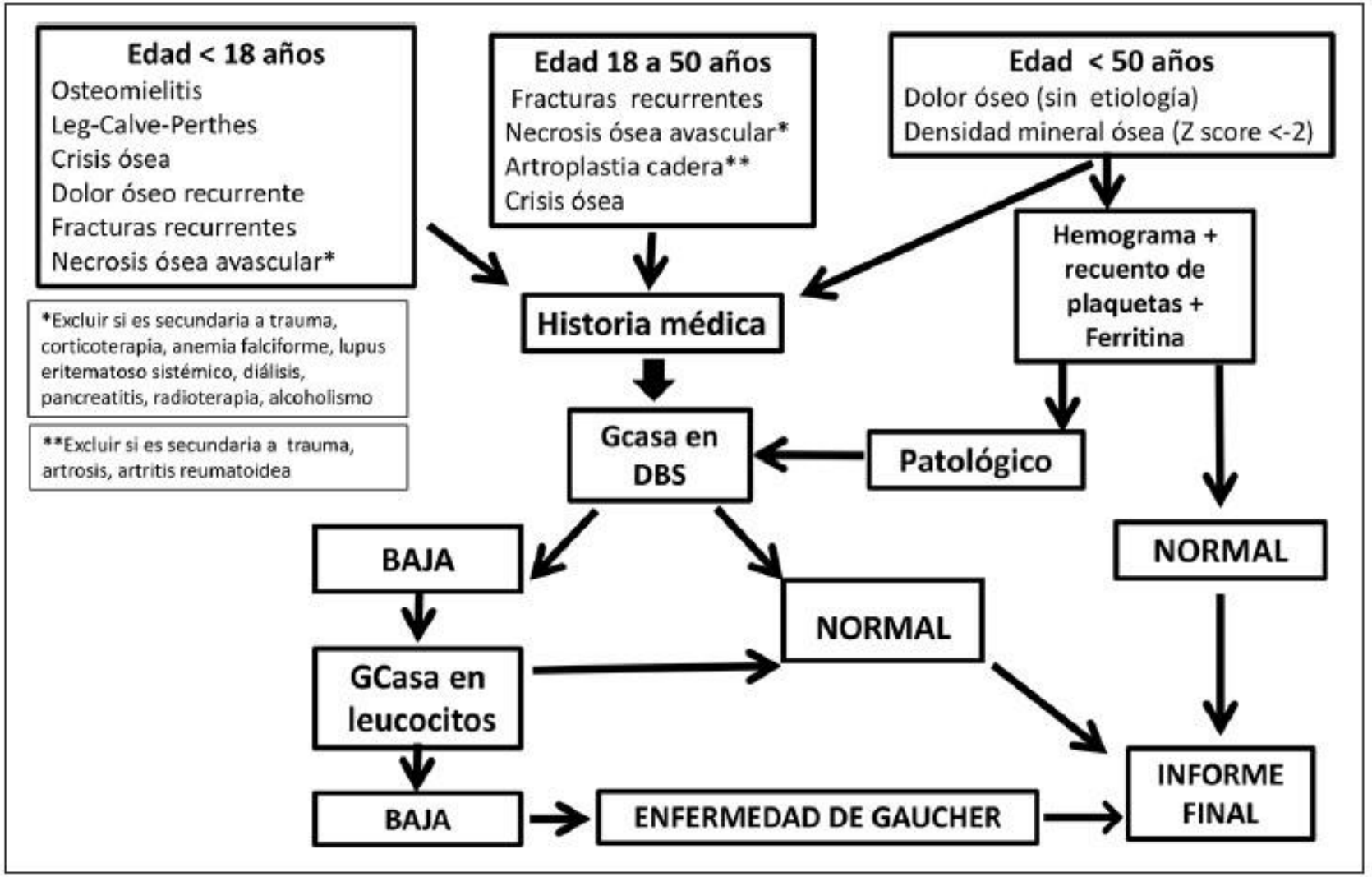
DIAGNÓSTICO TEMPRANO DE ENFERMEDAD DE GAUCHER MEDIANTE DETECCIÓN DE MANIFESTACIONES ÓSEAS

BEATRIZ OLIVERI[1], DIANA C. GONZÁLEZ[2], PAULA ROZENFELD[3], EMMA FERRARI[4], GLADYS GUTIÉRREZ[5]

[1]Laboratorio de Osteoporosis y Enfermedades Metabólicas Óseas, Instituto de Inmunología, Genética y Metabolismo (INIGEM), Facultad de Farmacia y Bioquímica, Hospital de Clínicas José de San Martin, UBA-CONICET, Buenos Aires, [2]Mautalén, Salud e Investigación, Buenos Aires, [3]IIFP, Departamento de Ciencias Biológicas, Facultad de Ciencias Exactas-CONICET, Universidad Nacional de La Plata, La Plata, [4]Hospital Samco, Villa Ocampo, Santa Fe, [5]Servicio de Hemato-oncología, Hospital Juan Pablo II, Corrientes, Argentina

En representación del Grupo de estudio Bone Involvement Gaucher Disease (BIG)

Fig. 1.– Algoritmo para el diagnóstico de enfermedad de Gaucher a partir de la afectación ósea



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¡Gracias!
Obrigado!
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