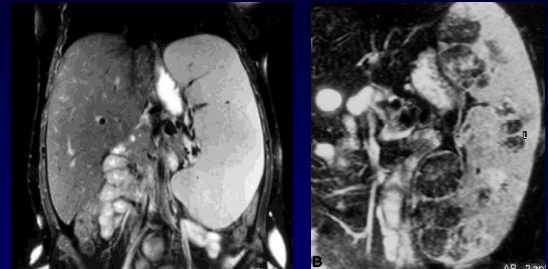


## Gaucher Disease: A (Rare) Differential Diagnosis in Hematology

Stephan vom Dahl, MD  
St. Franziskus Hospital  
University of Cologne  
Cologne, Germany



### Conclusion

- Gaucher disease is a not infrequent differential diagnosis in hematologic patients
- Symptoms could be: Splenomegaly of unknown origin and unexplained bone pain
- Gaucher cells in bone marrow may be absent, determination of enzyme activity in EDTA-blood is mandatory
- Enzyme replacement therapy is effective

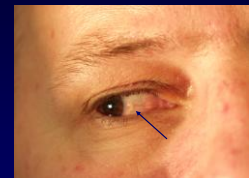
### A Male with Oligosymptomatic Splenomegaly

### , 57-Years-Old

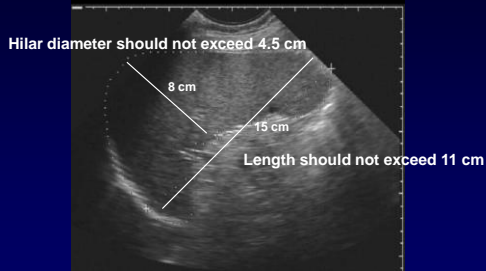
- Presents with pathologic blood count
- Easily tired, needs long rest during daytime
- Easy bruising and epistaxis
- Bone pain episodes with long bedrest as a child
- Knows that spleen is enlarged, but does not bother him

### Physical Examination

- Pingueculae both eyes
- Splenomegaly restricted to upper left quadrant
- Decreased mobility of both legs due to pain
- Otherwise unremarkable



## Abdominal Ultrasound: Splenomegaly

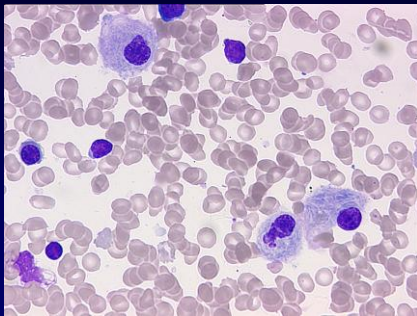


Splenomegaly (normal: 2 ml/kg body weight) is defined as a spleen volume > 500 mL

## CBC and Clinical Chemistry

- Hemoglobin 11.1 g/dL
- Platelets 36.000/ $\mu$ L
- WBC 3.830/ $\mu$ L
- Total protein 8.3 g/dL,  $\gamma$ -globulins 16.1 rel.%, MGUS IgG/kappa
- ESR 29 mm within 1<sup>st</sup> h
- Clinical chemistry otherwise unremarkable
- A bone marrow biopsy was done

## Gaucher Cells



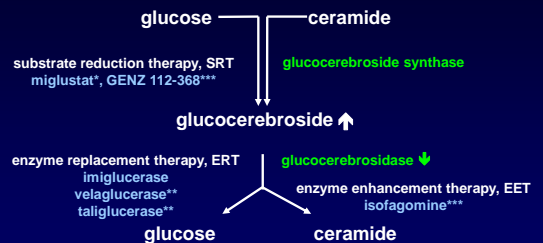
Courtesy: Eugen Mengel, Children's Hospital, University of Mainz

## The Diagnosis Was Secured by Measuring $\beta$ -Glucocerebrosidase Activity from EDTA-Blood

- The  $\beta$ -glucocerebrosidase activity in leucocytes was 1.1 nmol/(mg x h) (reference range 10-25)
- ACE, ferritin, TRAP were increased
- Chitotriosidase activity in plasma was massively increased to 6740 nmol/(mL x h), (reference range 0-200)
- Genotyping revealed the N370S/L444P mutation in the glucocerebrosidase gene, i.e. compound heterozygosity

## Pathophysiology and Classification

## Glucocerebroside Metabolism

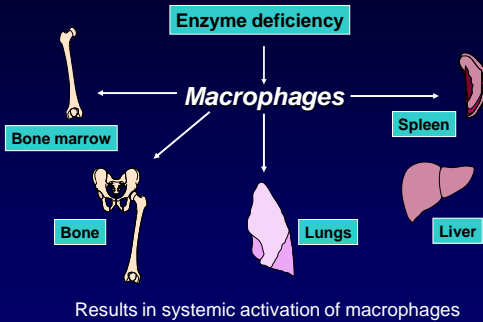


\*, approved for mild/moderate cases, when ERT is not possible

\*\* , approval pending

\*\*\*, phase II data pending

## Pathophysiology of Gaucher Disease



## M. Gaucher-“Colloidian Baby“ Due to Complete Lack of Glucocerebrosidase

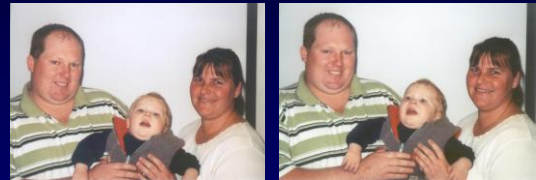


Image courtesy of Chris Hendriksz, Birmingham Childrens' Hospital

## Classification

- Non-neuronopathic, visceral (type 1):
  - Panethnic (prevalence 1:50,000)
  - Prevalence in Ashkenazi Jews 1:500
  - Primary manifestation possible at every age
- Neuronopathic (type 2 and type 3)
  - Type 2: Acute neuronopathic, death within first 2-3 years
  - Type 3: Chronic-neuronopathic, better prognosis

## Horizontal Gaze Palsy Is Characteristic for Neuronopathic Type

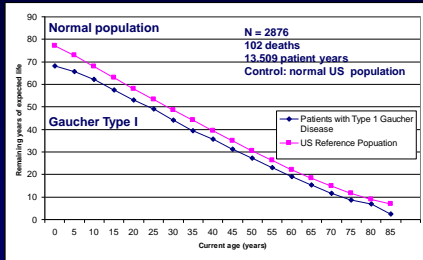


## Classical Type I Presentation

- Loss of power
  - Low platelets
  - Mild anemia
  - Splenomegaly
  - Bone pain reported upon thorough interview
  - Work-up not revealing classical causes
- ... mandates Gaucher disease as a differential diagnosis

## Natural History of Type I Gaucher Disease

## Life Span in Type I Gaucher Disease Is Decreased



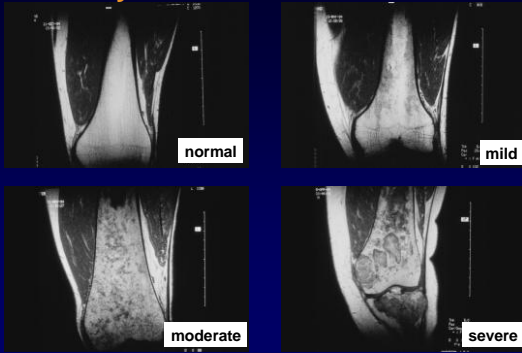
Weinreb NJ, et al. *Am J Hematol*. 2008;83(12):896-900.

## Prevalence of Malignancy in Gaucher Disease

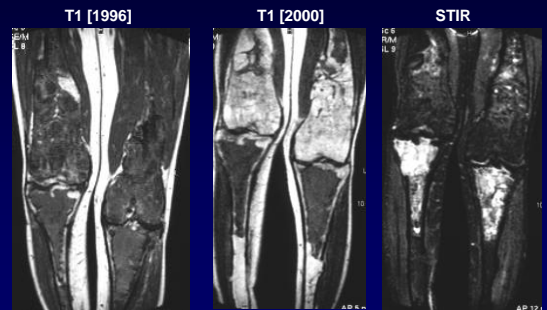
Category	Fold at Risk
Total tumors	2.5 *
Hematologic malignancies	12.7 *

de Fost M, et al. *Blood Cells Mol Dis*. 2006;36(1):53-58.

## Severity of Bone Marrow Infiltration



## Bone Infarctions Contribute Significantly to Morbidity in Gaucher Patients



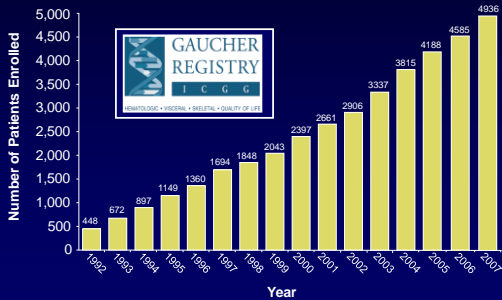
## Atypical Manifestations



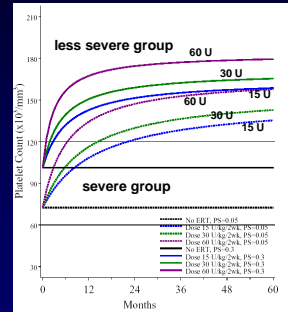
Amyloid L Depositions

## Therapy of Gaucher Disease

## Standard Of Care: Biweekly Infusions of Imiglucerase, Dose Adjusted to Severity of Disease



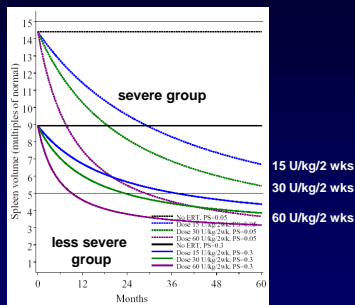
## Platelet Count Dose-Response



Control group

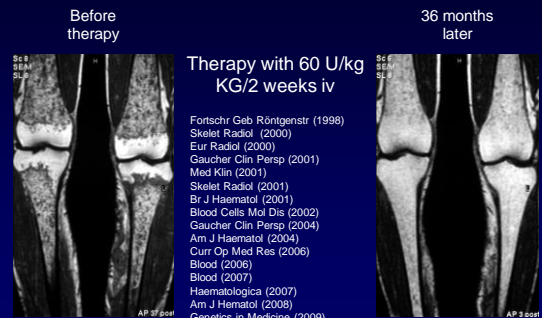
Grabowski, GA, et al. *Genet Med.* 2009;11(2):92-100.

## Spleen Volume Dose-Response

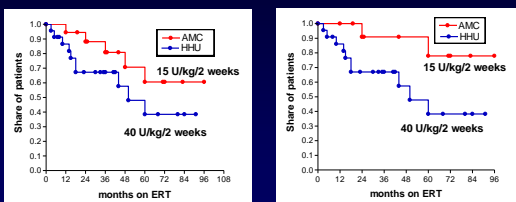


Grabowski, GA, et al. *Genet Med.* 2009;11(2):92-100.

## Bone Marrow Response in ERT



## Improvement of MR Bone Marrow Burden ( $\Delta$ BMB = 2, BMB=semiquantitative MR-Score)



Baseline BMB 2-8

Baseline BMB  $\geq$  6

de Fost M, et al. *Blood.* 2006;108(3):830-835.  
Hollak, CE, et al. *Blood.* 2007;109(1):387-388.

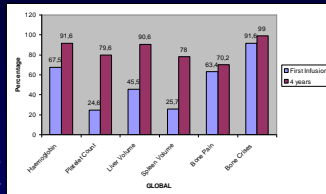
## Goals of Enzyme Replacement Therapy Can Be Stratified According to Their Clinical Probability

- Very likely
- Probable
- Questionable
- Almost never

Schmitz J, et al. *Haematologica.* 2007;92(2):148-152.

## Numbers Needed to Treat to Reach Specific Goals Within 4 Years

Thrombocytopenia	1.8
Splenomegaly	1.9
Hepatomegaly	2.2
Anemia	4.1
No bone crisis	13.5
Bone pain absent	14.7



Weinreb N, et al. *Am J Hematol*. 2008;83(12):890-895.

## Other Hematologic Manifestations

- Clearly increased prevalence of hematologic neoplasias
- Prevalence of solid tumors slightly increased
- Polyclonal and monoclonal MGUS associated
- Sometimes autoimmune hemolytic anemia
- Disorders of coagulation associated
- Amyloidosis as a long-term complication

Zimran et al. (2005) *Hematology* 10, 151-156

## Summary

- Clinical presentation of Gaucher disease has shifted from hemato-visceral manifestations to bone disease with different atypical findings
- Splenomegaly is almost never absent
- Different hematologic complications may arise and be associated
- If treated early enough, most manifestations in type 1 respond well to enzyme supplementation

## The Köln Group



C. Rader, M. Seimel, S. vom Dahl, S. Schütz, K. Heger

Next International Cologne Gaucher Workshop: Feb. 10, 2010



Images courtesy of S. Sozin, Moscow  
5<sup>th</sup> Gaucher Workshop, Cologne, 2009