# Gorham-Stout disease (GSD): a Diagnostic and Treatment Protocolt

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## BACKGROUND and AIM

**P3-646**

Gorham-Stout syndrome (GSD) is a rare disorder characterized by lymphangiomatosis, invasion of soft tissues, osteolysis associated with severe bone morbidity and potentially lethal in the presence of chilothorax. Although bone lesions are due to abnormal vessels proliferation, new lines of investigations point out the role of osteoclastogenic cytokines.

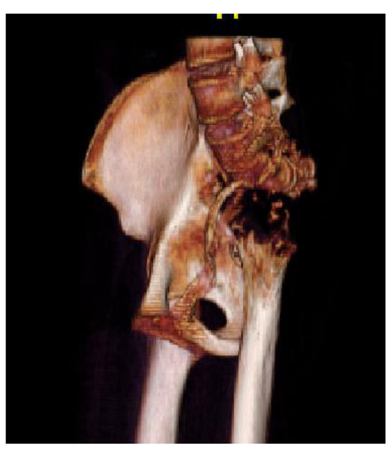
As the management of GSD is not univocal and outcomes are unpredictable we build a multifaced protocol in order to study its natural history, biomarkers of disease severity and to treat the patients uniformly.

## SUBJECTS and METHODS

n=7 patients (5M and 2F, 3 mts-26.0 yrs of age) with GSD (dgn by biopsy) underwent at baseline, after 6 months and than yearly:
1.clinical examination
2.imaging evaluations (Total Body -TB- and spine DXA and STIR Total Body MRI)
3.biochemical (Ctx, BAP, PTH, 25OHD, D-Dimer);
4.karyotype, CGH-array
Based on clinical status they were treated with bisphosphonates (BP) and/or Interferon (INF):
1. PAM: 1 mg/kg for 3 d/4 mts (max 30 mg/dose) or ZOL: 0,025 mg/kg T0 and +6 w; then 0,05 mg/kg/3mts (max 4 mg/dose)
2. If chylotorax: INFalfa2b 1500000 U/m$^2$ every other day

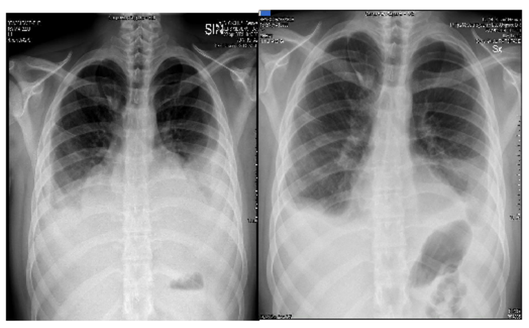
**Table 1. Age at diagnosis, bone involvement, symptoms (*C=chylothorax) and therapy in 7 patients with GSD**

| Sex | Age at diagnosis/ Ist evaluation | Bone | Focal/ Multifoc. | Ist Signs/ symptoms | C* | Therapy | FU/re-activation |
|---|---|---|---|---|---|---|---|
| M | 24,0/26,0 | 2 Ribs, clavicle | Focal ext | Cutaneous angioma swelling, Pain, Dyspnea | yes | INF 1y+6m/ hypolip diet/ ZOL 6m | 5 yrs/ C*n=3, last in 2012 |
| M | 15,8/16,3 | Sternuum, ribs | Focal ext | Toracic pain, Dyspnea | yes | INF | 4,8 y |
| M | 12,0/17,3 | Femur, ilium, ischium, pubis | Mult | Lameness, Pain, multiple fragility fracture (2005-2009, hypertrophy L limb, Dyspnea | yes | 2005-2007 PAM, 18 m 2009 PAM-ZOL, INF | **5 y** C*n=3, last in 12.2010 |
| M | 1,2/1,9 | Ulna | Focal | Local swelling, Pain | no | PAM | 3,5 y |
| F | 10,8/12,4 | Clavicle, 2 ribs, cranium | Mult | Fragility fracture, Dyspnea, Pain | yes | 2011-2012 PAM 12 m INF+ZOL 2013 | 4,5 y Rib-clavicle n=1 07.2013 Cranium? |
| F | 4,2/4,8 | Scapula, humerus | Focal | Cutaneous angioma | no | - | 2 y |
| M | 0,0/0,6 | Cranium | Focal ext/Mul | Laterocervical swelling, local eritema, noisy breath, dyspnea | no | ZOL | **0,7 y** |



**Subjects**
•n=7: osteolysis at baseline (clavicle n=1, ribs n=2, femur n=1, sternum n=1, humerus n=1, scapula n=2, ulna n=1, cranial basis n=1)
•1 osteolysis lately (parietal bone)
**•n= 3 pathological fractures before therapy start (clavicle n=1F, hip and femur n=1M, rib n=1M), 44%**
**•n=4 chylothorax, 57%**

**Responses to therapy**
- During BP:reduction of bone pain till resolution
- During BP+INF2b: Reduction/resolution of chilotorax



**DXA results**
- n=1M and 1F: reduced TB BMD for age/sex
- n= 2M and 1F: reduced spine BMD (Z-scores between – 2.8 and –1.1)
- subjects on BP displayed an increase in BMD of about 1 Z-score during therapy

**Figure 1. a. BMD TB and b. Spine BMD response to BP in 1 pts with multifocal GSD and femural fragility fracture**

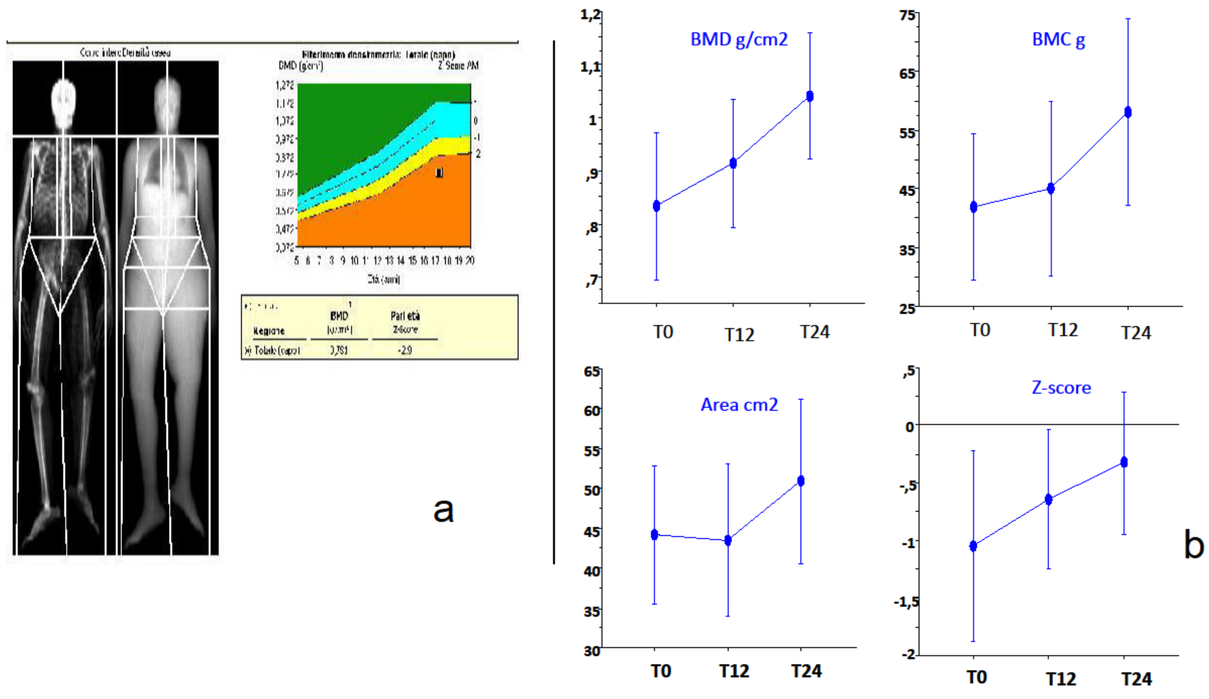
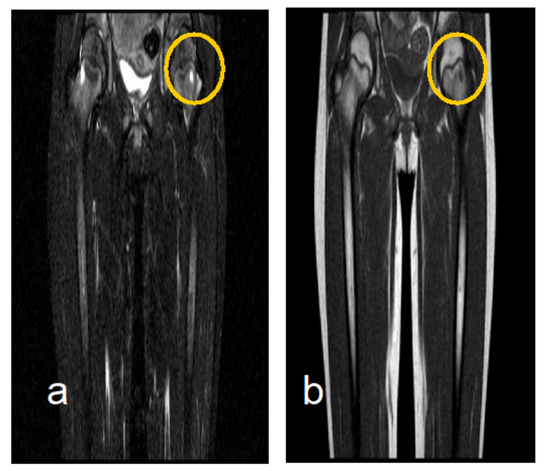
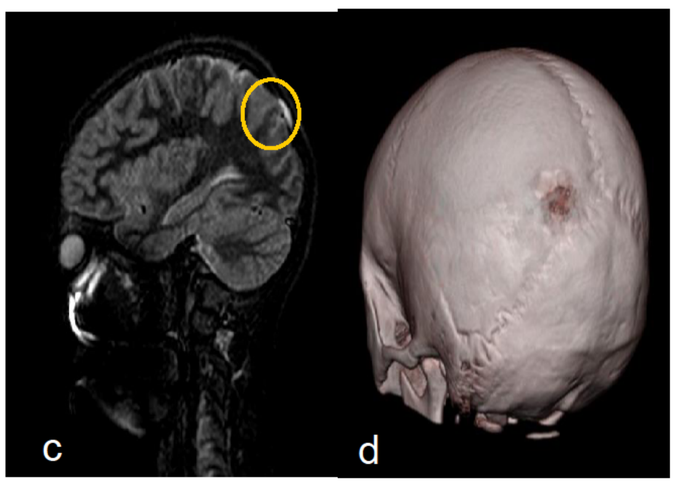



**Figure 2. a. Hyperintensity in STIR (a) Hypointensity in T1(b)**

**TB STIR MRI studies**
- Non specific involvement of multiple skeletal sites far from the primary localization in 2 pts (Figure 2, panel a. and b)
  - reduced/ increased during FU

**Figure 3. a. Hyperintensity in STIR (c) TC (d)**



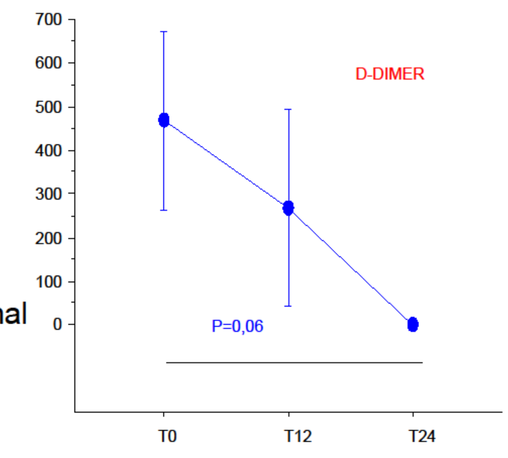




- 1 new focus of disease (c) in 1 pts with multifocal disease, confirmed by CT (d) (Figure 3, panel c. and d)

**Bone markers did not change during acute or re-activation of GSD; only the D-Dimer was increased during acute phases of GSD (Figure 4.)**

**Genetic studies**: Karyotype and CGH-array were normal

**Figure 4. D-Dimer during 24 mts follow-up**




## CONCLUSIONS

- In GSD , control of bone pain and chylothorax was obtained with BP and INFa2b;
- New acute phases of GSD occured in patients with extended focal forms of GSD (3 out of 4 pts)
- DXA showed reduced BMD in 3 out of 4 pts with severe forms of GSD (systemic bone reabsorbtion? Other factors?)
- D-Dimer might be useful during follow-up as a vascular malformation marker (bone markers seems not to have a prognostic role)
- The specificity of STIR MRI need to be confirmed; it still be useful in defining focality/multifocality of disease: different follow up?
- Exome Sequencing of the DNA of the lesions might be useful

ESPE 2015 646--P3
Bone
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DOI: 10.3252/pso.eu.54espe.2015
Poster presented at: 54th Annual Meeting 1-3 October ESPE 2015 BARCELONA European Society for Paediatric Endocrinology
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