FORSCHUNGSZENTRUM FÜR DAS KIND (FZK)

KINDERSPITAL ZÜRICH

Echocardiographic Findings in 41 Children with Various Lysosomal Storage Disease

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Background

- Lysosomal storage disorders (LSD) are a group of >40 diseases involving multiple organs
- Deficiency of lysosomal enzymes and other dysfunctions of lysosomal biology
- Cardiac involvement includes
  - Valve thickening, hypertrophy, pulmonary hypertension
  - AV block, arrhythmias, SCD

Linhart et al. Heart 2007

Namdar et al. AJC 2010

Background

- Heterogeneous phenotype – residual enzyme activity
- Various possible therapies
  - Enzyme replacement therapy, where available
  - Bone marrow transplantation (MPS I, <2 years)

- Clinical manifestation in Mucopolysaccharidosis (MPS) depends on subtypes:

Leal et al. CTY 2010

- Is the cardiovascular involvement in other lysosomal storage disorders in children comparable to MPS?
- **Aim of the study: characterize and compare the echocardiographic findings in various groups of LSD**

Methods

- Review of the most recent echographic exam of all patients with LSD from 1/1994 to 5/2011

- All patients with genetic or enzymatic evidence for
  - Anderson-Fabry disease (including males and females)
  - Mucopolysaccharidosis (MPS)
  - Mucolipidosis II and III, I-cell disease (ML)
  - Glycogenosis II (GLII), (Pompe disease)

- Review of complete patient history
  - Symptoms
  - Outcome
  - Therapy: enzyme replacement and bone marrow transplant

Methods - Definitions

- Echocardiography: chamber dimensions (LV, LA) expressed as Z-score/body surface area, Z>+2=enlarged

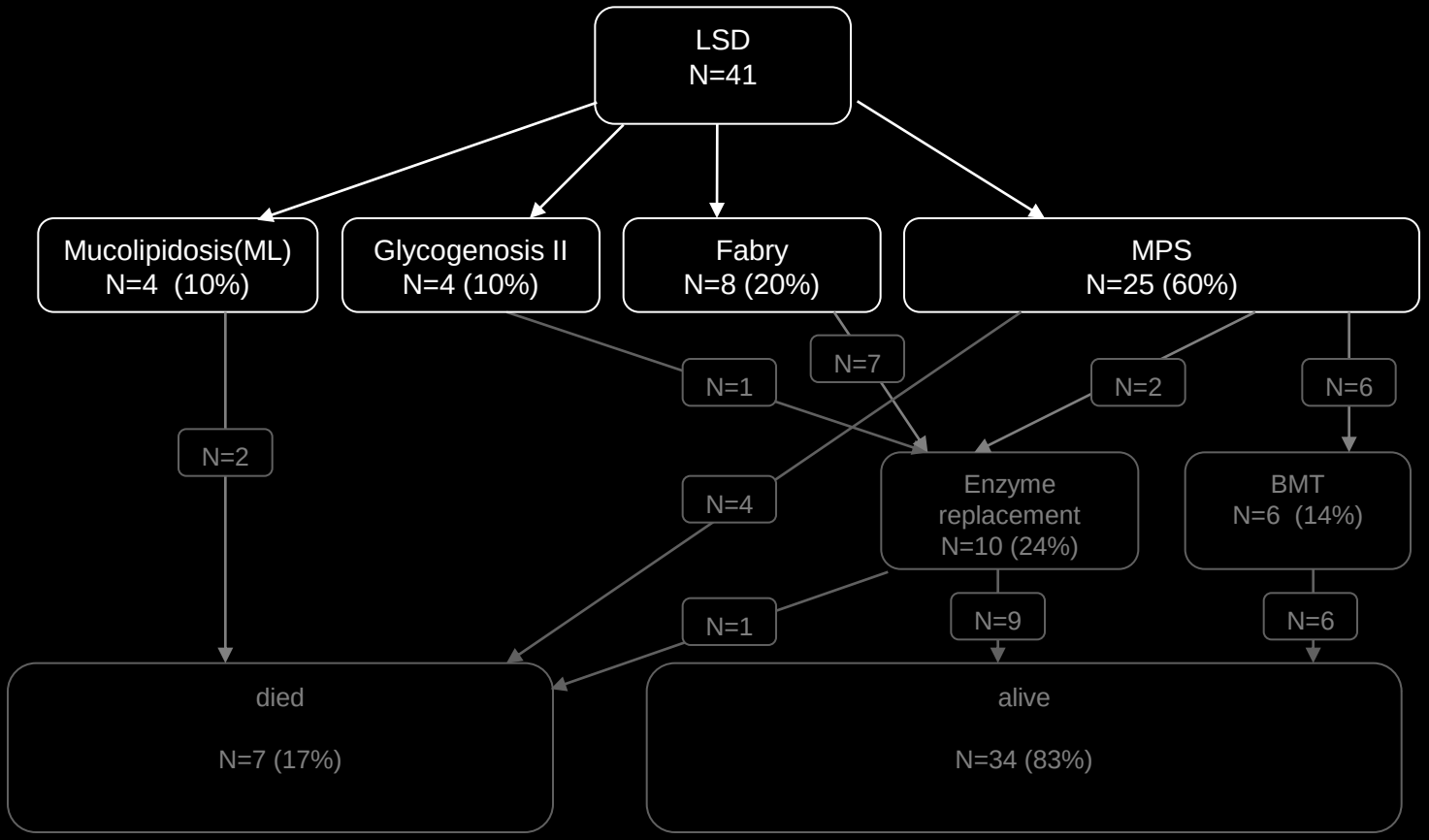
- Hypertrophy: Left ventricular mass index (LVMI)>Z-score +2
- Abnormal diastolic function: age specific,
  - at least one abnormal parameter (IRT, PvenAR, e/e', TDI)
  - Regurgitation mitral/aortic valve according ASE-Guidelines
  - Pulmonary hypertension, non invasive, SPAP>35mmHg

- Statistics
  - Categorical: Fisher and $Chi^{2,}$
  - Continuous: ANOVA (Newman-Keuls corrected)

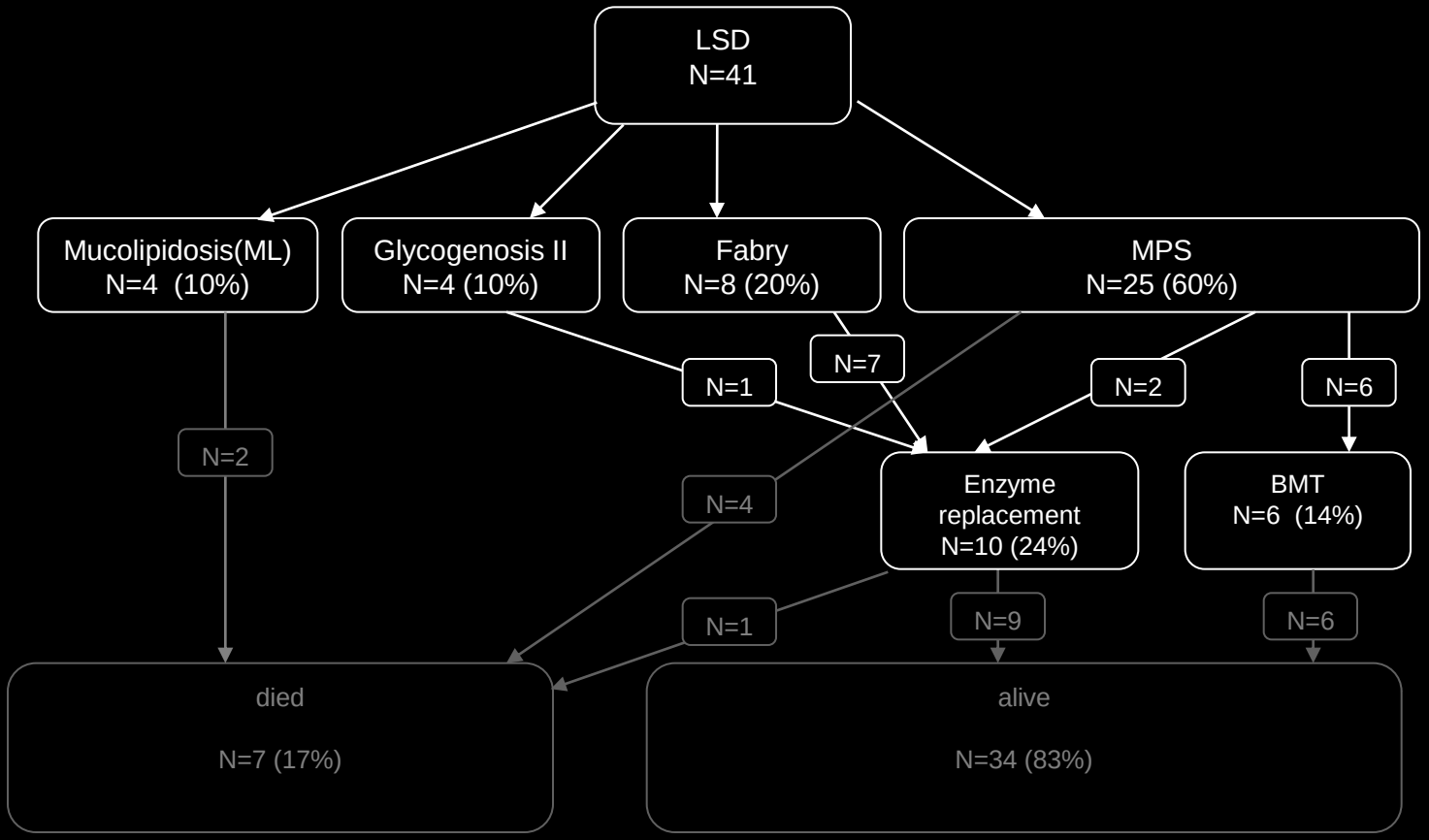
Results – clinical characteristics

	All patients	MPS	Fabry	Others (ML, Pompe)	P
N	41	25 (60%)	8 (20%)	8 (20%)	
Age(y)	11.4 (2-27)	11.5 (2-19)	10.8 (10-17)	6.5 (2-27)	NS
Male	17 (41%)	14 (56%)	1 (13%)	2 (25%)	NS
F/U(y) mean (SD)	7.3 ±4.7	8.5 ±4.0	3.5 ±1.2	7.5 ±7	**0.02** **MPS vs Fabry**
NYHA I **NYHA II** **N/A (orthopedic problems)**	30 (73%) 4 (10%) 7 (17%)	17 (68%) 3 (12%) 5 (20%)	7 (87%) 0 (0%) 1 (13%)	6 (75%) 1 (12.5%) 1 (12.5%)	NS

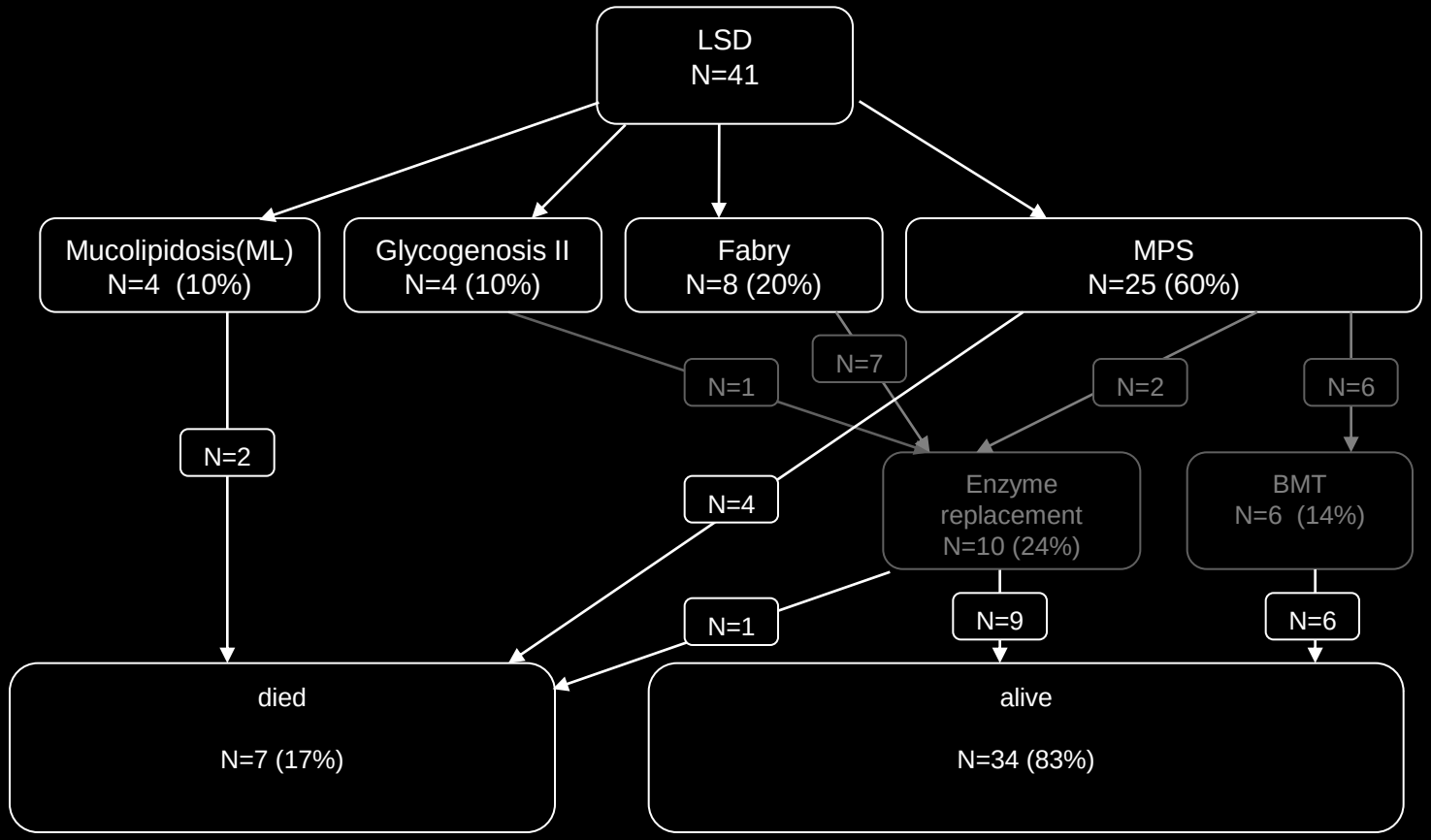
Results – therapy and outcome



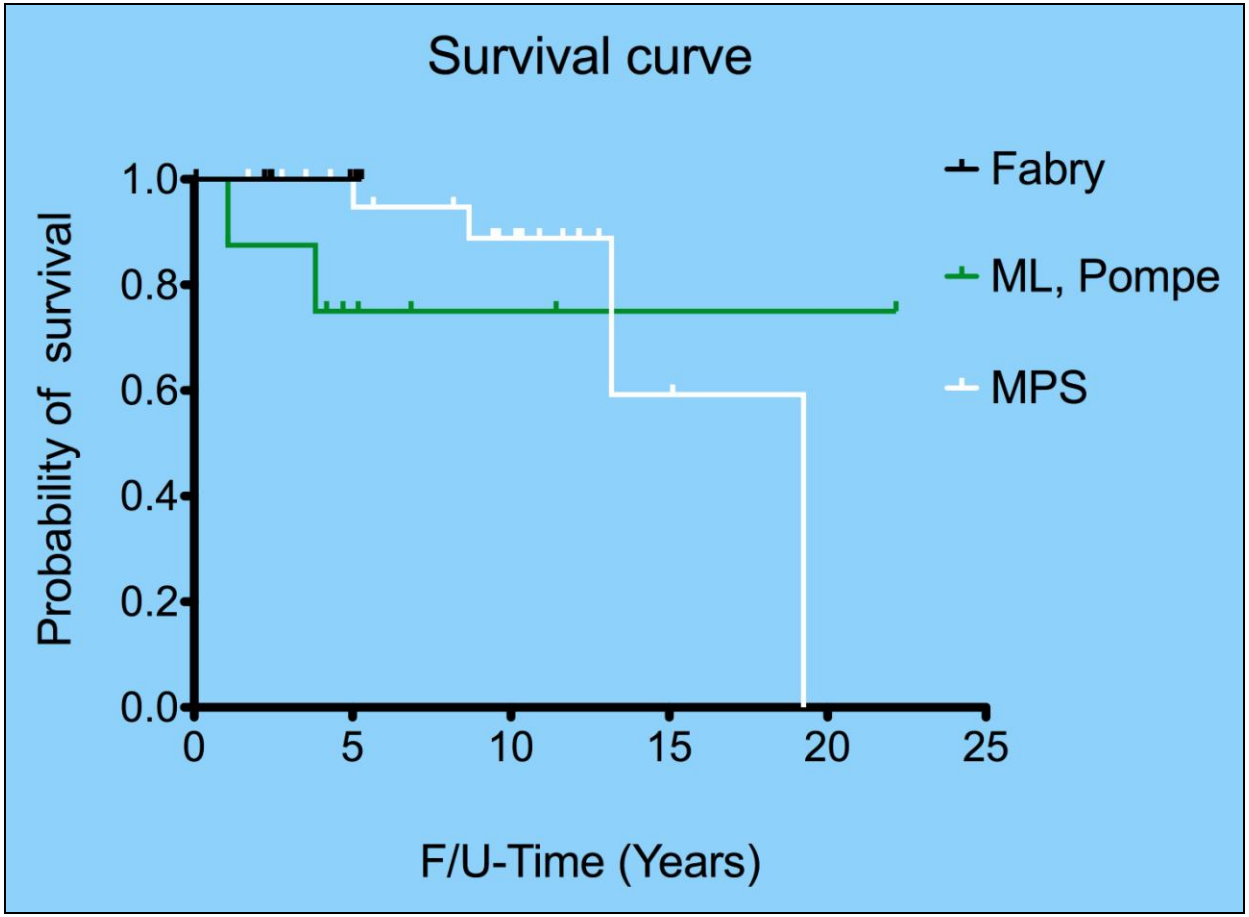
Results – therapy and outcome



Results – therapy and outcome



Results - survival

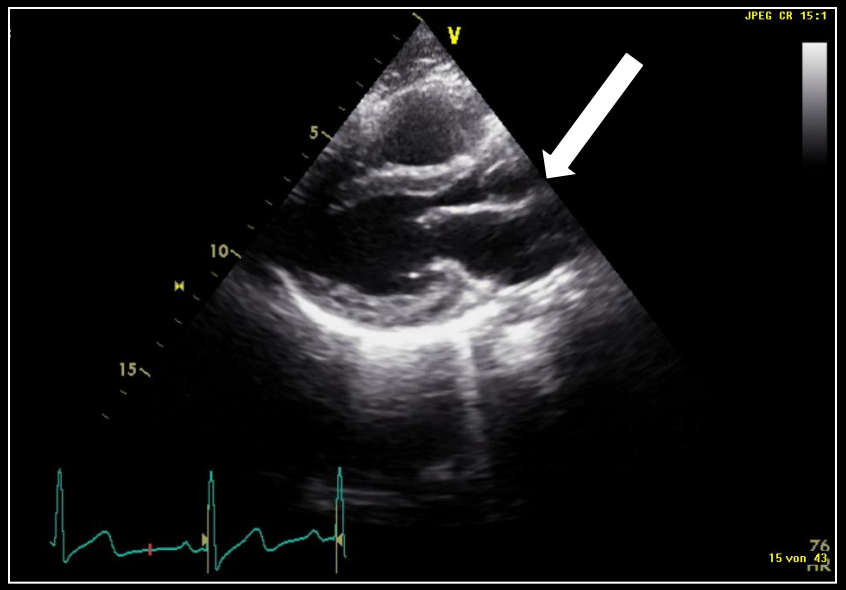


Results – echocardiography

VALVES	All patients	MPS	Fabry	Others (ML, Pompe)	P
Abnormal mitral valve	**20/41 (48%)**	17/25 (68%)	**0/8 (0%)**	3/8(38%)	MPS vs others= NS
		P=0.0009	**P=NS**		
>mild mitral regurgitation	**3/41 (7%)**	2/25 (8%)	0/8(0%)	1/8(12%)	NS
Abnormal aortic valve	**18/41 (46%)**	15/25 (64%)	0/8 (0%)	3/8 (38%)	MPS vs others= NS
		P=0.004	**P=NS**		
>mild aortic regurgitation	**2/41 (5%)**	2/25 (8%)	0/8 (0%)	0/8 (0%)	NS

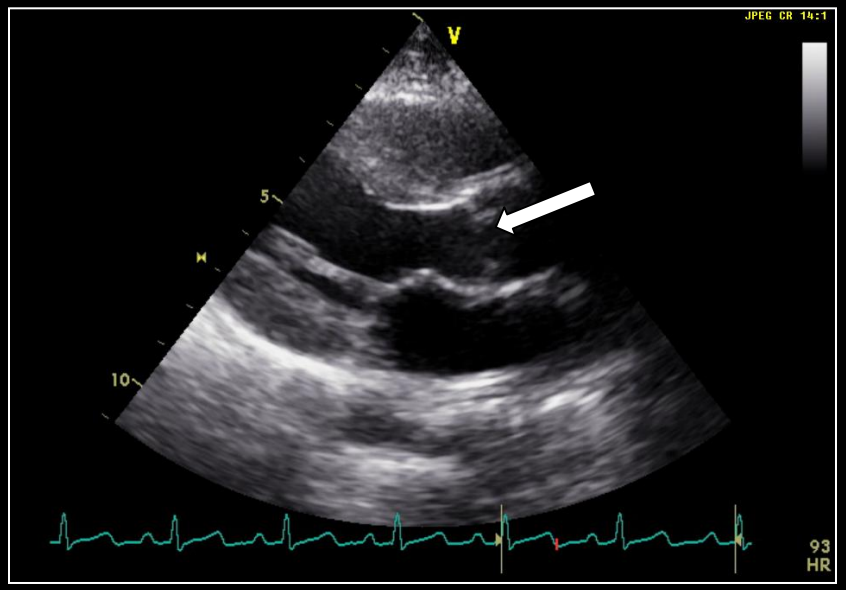
Mucopolysaccharidosis (MPS) I

13-year old girl



2-times Bone Marrow Transplantation (BMT)
2/00, 6/01

12-year old brother

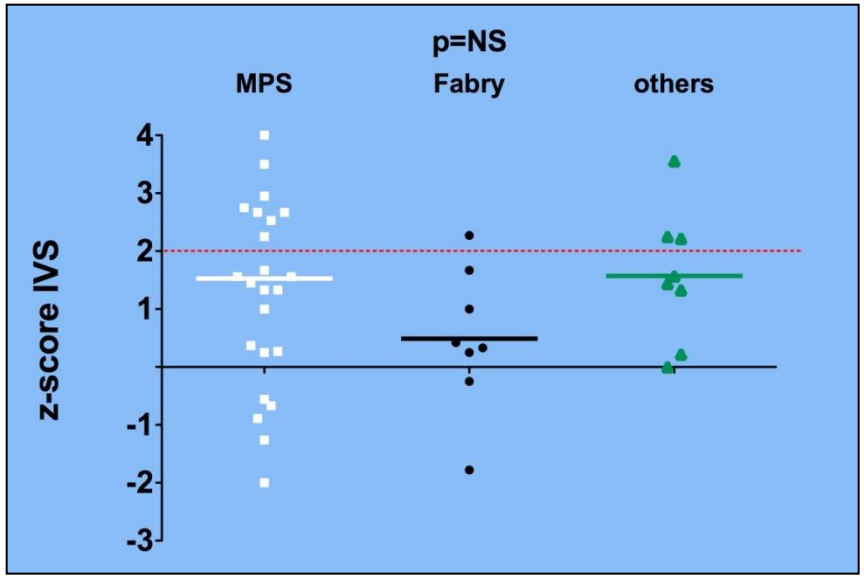


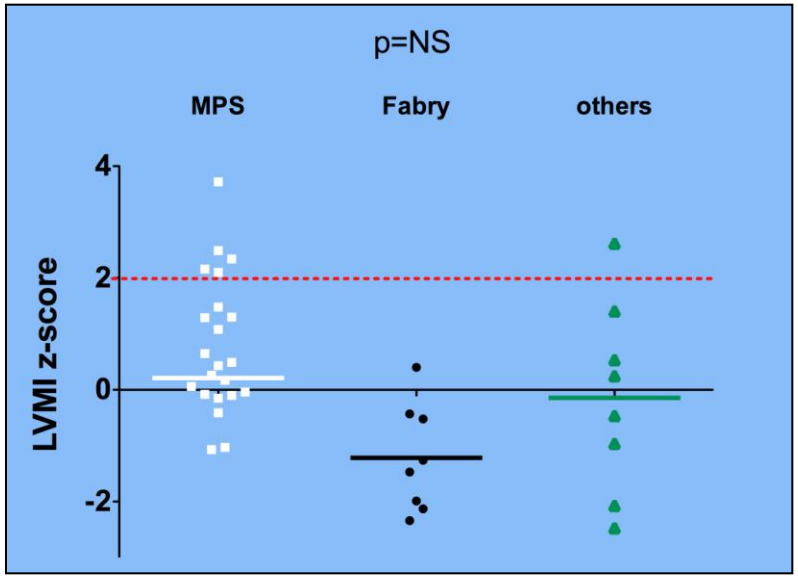
2-times Bone Marrow Transplantation (BMT)
5/00, 12/00

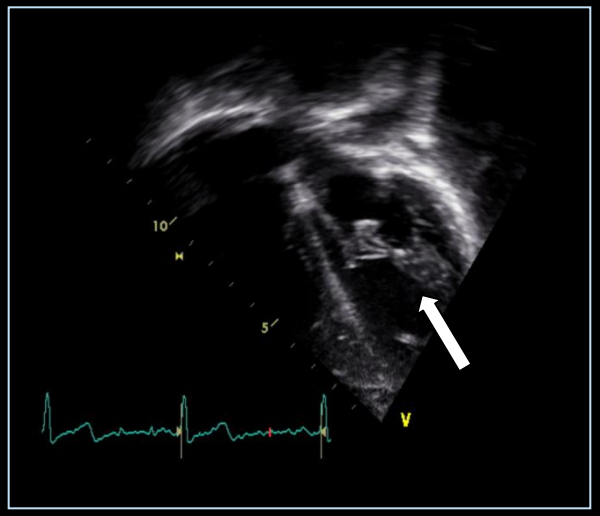
Results –hypertrophy and function

	All patients	MPS	Fabry	Others (ML, Pompe)	P
N	41	25 (60%)	8 (20%)	8 (20%)	
LVMI/m^2 **LVH**	71 ±20 7/41 (17%)	73.8 ±21.0 5/25 (20%)	62.7 ±9.2 0/8 (0%)	70.3 ±20.3 2/8 (25%)	NS NS
EF (mean±SD)	59.6 (±4.5)	59.2 (±4.2)	57.5 (±3.5)	62.6 (±5.2)	0.06
Pulmonary hypertension	2/19 (11%)	2/9 (22%)	0/6 (0%)	0/4 (0%)	NS
Diastolic function abnormality	4/16 (25%)	3/7 (43%)	0/5 (0%)	1/4 (25%)	NS

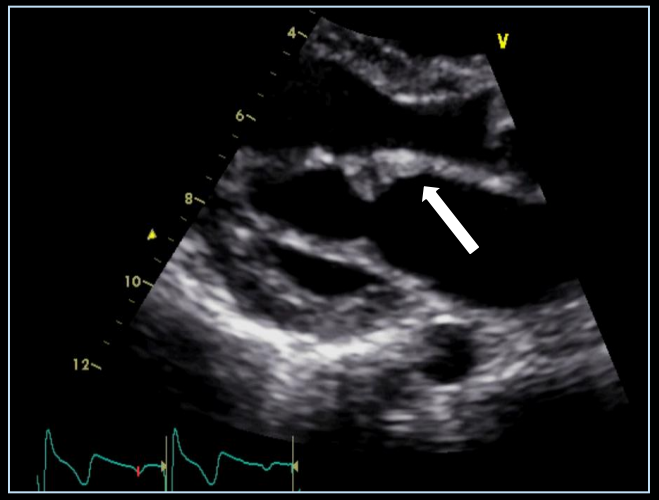
Results- interventricular septum left ventricular mass



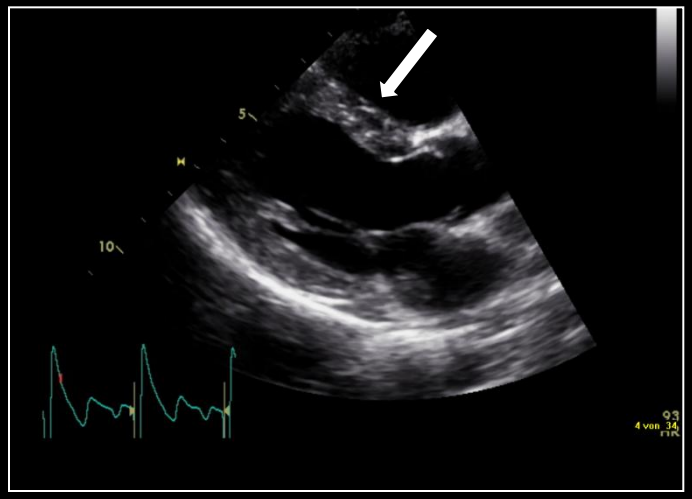




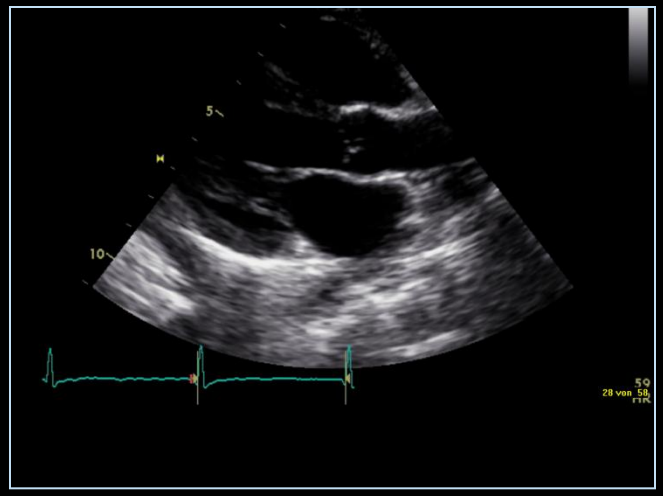
18-year old woman– MPS IV-ERT



14-years old boy – MPS Type II (Hunter)



13-year old boy - Pompe disease



7-year old girl - Fabry disease

Summary

- Echocardiographic anomalies are observed in approximately 50% of all cases
  - Valve anomalies predominate in MPS
  - Normal systolic function
  - Diastolic function abnormalities can be present
  - LVMI higher in 20% of MPS-patients, not in Fabry patients

- Significant echocardiographic abnormalities were not present in Fabry disease in our pediatric cohort
  - Shorter F/U?
  - 83% female carriers > males
  - although earlier onset is described for males in adulthood

  (X-chromosomal inheritance)

Zarate et al, The Lancet 2008

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Conclusion

- In the pediatric age group, cardiovascular involvement is especially relevant in MPS, where valve anomalies predominate
- Routine assessment is recommended in all patients with or without enzyme replacement therapy
- Thanks for your attention!