FABRY DISEASE

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Lysosomal Storage Disorders (LSDs)

• Include at least 50 distinct single gene disorders
• Each one results from;
  – a deficiency of a particular lysosomal protein/activity,
  – from non-lysosomal activities that are involved in lysosomal biogenesis or protein maturation
• Incidence as a group is about 1:7,000-9,000
Fabry Disease

- Lysosomal α-galactosidase A deficiency
- Incidence; 1/40,000-117,000 births – male
- GLA gene, X chromosome
- GLA gene mutations >450
- Frequency
  - **Australia**: 1/117,000 (hemizygous)
  - **Holland**: 1/476,000 (prevalence)
  - **UK**: 1/366,000 (prevalence)
  - **Italia**: Newborn screening: 1/3,100 newborn
  - **Taiwan**: Newborn screening 1/1,500 male newborn
  - **Türkiye**: HD patients - 1.7/1000
Screening for Fabry disease in patients undergoing dialysis for chronic renal failure in Turkey: Identification of new case with novel mutation

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d Ankara Keçiören Dialysis Center, Ankara, Turkey

- 1136 dialysis patients
- %52.5 male
- Mean age 56.46±15.85
- Low enzyme activity in 12 pts with DBS
- Positive enzymatic and genetic tests in 2 males
- Prevalence 0.17%
- New mutation (homozygous c.638C>T (p.P214S) missense mutation, in exon 5
- Family screening– 6 new patients
## Screening for Fabry Disease Among Patients with ESRD–1

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<th>Dialysis study</th>
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### Screening for Fabry Disease Among Patients with ESKD–2

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<th>Renal transplantation Study</th>
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DBS, dried blood spot; ESRD, end-stage renal disease; L, leukocytes; Tx, transplantation.
Pathophysiology of Fabry Disease-1

**Glycosphingolipid metabolic pathway**

Absent/deficient activity of lysosomal exoglycohydrolase α-galactosidase A

As little as 5–10% of residual enzyme activity seems to be sufficient to prevent clinically significant substrate accumulation.
Pathophysiology of Fabry Disease-2

- Inability to catabolize certain glycosphingolipids
  - Globotriaosylceramide (Gb3)
  - Galabiaosylceramide

  results in progressive accumulation of Gb3 in the vascular endothelium and visceral tissues
  (Ganglion cells, heart, kidney, eye and many other organs)

Pathophysiology of Fabry Disease-3

- α-galactosidase A deficiency
- Glycosphingolipid accumulation
- Inflammation, fibrosis, hypoperfusion
- Organ dysfunction
- Morbidity and mortality

Zarate et al, Lancet 2008; 372: 1427–1435
Natural Progression of Fabry Disease

- Heart involvement
- Hearing loss
- CNS disease
- Angiokeratomas
- Renal involvement
- GI involvement
- Eye involvement
- Acroparesthesias

CNS, central nervous system; GI, gastrointestinal.
System involvement in Fabry disease (%)

- Eye: 23%
- Kidney: 17%
- Skin: 13%
- Periph. Nerve: 13%
- GI: 9%
- CNS: 8%
- Bone: 5%
- Lung: 3%
- Heart: 23%
Misdiagnosis in Fabry cases

- CKD – unknown etiology: 22%
- Psychiatric: 34%
- Skin disease: 11%
- Hypertension: 11%
- Thrombotic disease: 11%
- Rheumatic disease: 11%
- CKD – unknown etiology: 22%

Colchicine resistant FMF cases
Fabry Disease Diagnosis

Enzyme analysis
- Leukocyte (7-10 ml EDTA blood)
- Dried blood sample

Genetic analysis
- 5 cc EDTA blood
- Dried blood sample
α-gal A levels in Male and Female patients

• Males
  – Low α-galactosidase A activity

• Females
  – α-galactosidase A activity may be normal in affected females
  – Definitive diagnosis with GLA gene sequence analysis
X-inactivation in Fabry Disease


Non-random

Random

% 50

% 0

% 0

% 0

% 0

% 50

% 50

% 50

% 0

non-affected

affected
Fabry Disease - Diagnosis

• Urine Gb3
  – Diagnostic in 95% of female heterozygotes with classical disease
  – ERT response evaluation in male patients

• Plazma Gb3

• Plazma lyso-Gb3 (globotriaosylsphingosine, deacylated Gb3)
  – Male patients, early increase (200-400X)

• Malta cross in phase contrast microscopy

Obvious need for a reliable and validated biomarker!
CKD – unknown etiology
Proteinuria/albuminuria
eGFR<90 ml/dk/1.73 m$^2$

<50 yrs males, all females

Hot/cold intolerance
Anhydrosis
Acroparesthesia
Angiokeratoma?

Males
Enzyme assay

Females
Gene sequencing

ERBP Recommendations for FD screening

Clinical Spectrum of Fabry Disease

- Fatigue
- Dizziness
- Hearing loss
- Heart problems
- Airflow limitation
- Kidney problems
- Acroparaesthesia
- Peripheral neuropathy
- Hypohydrosis
- Lymphoedema
- Eye abnormalities
- Vasculopathy
- Stroke
- Neuropsychiatric and psychosocial issues
- GI problems
- Angiokeratomas
- Low exercise tolerance

Fabry Disease  Clinical Heterogeneity

Koca et al, Genotype-Phenotype Correlation in Turkish Patients with Fabry Disease- Unpublished
Cardiac Involvement

- Left ventricular hypertrophy
- Valvular disease
- Coronary artery disease
- Congestive heart failure
- Aortic root dilatation
- Diastolic dysfunction
- Disrythmia
Neurological Symptoms in Fabry Disease

• Observed in up to **84%** of male and **79%** of female patients

• Manifestations span the entire nervous system and may involve:
  
  – **Central nervous system**
    • Cerebrovascular manifestations (stroke, TIA)
    • Psychiatric symptoms (depression, fatigue, cognitive impairment)

  – **Sensory organs**
    • Ocular and auditory symptoms

  – **Peripheral nervous system**
    • Neuropathic pain (acroparesthesia and pain crises)
    • Autonomic dysfunction (impaired sweating and temperature sensation)

Depression and Quality of Life

• **Depression**
  – Depression: 46 %
  – Severe clinical depression: 28 %

• **Quality of life**
  – Nearly all studies show significantly reduced QoL
  – Almost all areas of daily living are affected by the illness itself or by its psychosocial consequences.
  – Done by SF-36, EuroQoL and MMPI-2 questionnaires
Ocular Involvement-1

• **Corneal opacities (Cornea verticillata)**
  – Most common and early ocular findings
  – «Helezonic» in shape
  – Generally do not effect vision
  – Generally seen in both males and females
  – Easily recognized by “slit-lamp”
Ocular Involvement-2

Cataract
- Seen in about % 30.
- Generally anterior or posterior subcapsular (Fabry cataract)

Tortuosity of vessels
- Mild to marked tortuosity of the conjunctival and retinal vessels

Germain DP. Orphanet J Rare Dis. 2010;5:30.
Dermatologic Involvement

• Hypohydrosis or anhydrosis
• Hot/cold intolerance
• Angiokeratomas
  – Red-purple raised skin lesions (angiomas)
  – Generally found on the buttocks, groin, umbilicus and upper thighs, also sometimes on mucosal areas
Renal involvement in Fabry disease

• Second most common reason for death in males

• Renal manifestations occur
  – early in life in a significant proportion of children
  – in many women (≈ 20%)
  – in most of men (≈ 50%)

• Disease severity increases with age

• Ultimately progress to ESKD in nearly all males and some female patients

• Lesions result from Gb3 deposition in
  – Glomerular endothelial cells
  – Mesangial cells
  – Interstitial cells
  – Podocytes
  – Tubululary cells
  – Renal arterioles
Multiple concentric lamellar ultrastructure in podocyte cytoplasm (EM, 21.000X) «ZEBRA BODIES»

Podocyte damage may be the key event in the development and progression of Fabry nephropathy

- Median age: 12 (4-19 yrs), 14 pts, GFR normal

- Correlation between age and podocyte GL3 inclusion volume density and progressive increase in food process thickness – correlated with proteinuria

- No correlation between age and endothelial/mesangial inclusion volume density

- Decrease in endothelial fenestration

- Podocyte food process effacement in children without proteinuria

Progression in renal disease

- Microalbuminuria, proteinuria, hyperfiltration (2nd-3rd decade)
- Isostenuria, tubular dysfunction
- Progressive deterioration (fibrosis, sclerosis and tubular atrophy), azotemia (3rd-5th decade)
- End-stage kidney disease (4th-5th decade)
Progression of Nephropathy in Untreated Patients

- Cumulative percentage of male patients developing proteinuria, CRI and death, with increasing age

Branton MH, Medicine (Baltimore) 2002;81:122-38
Progression of Nephropathy in Males and Females

- Of 366 patients (201 males, 165 females) in FOS, ESKD was present in 17% of males and in 1% of females.

- In the Fabry Registry, a total of 213 patients [186 of 1,359 males (14%) and 27 of 1,353 females (2%)] received renal replacement therapy at a median age of 38 years.

Basal eGFR

The goals of treatment in Fabry Disease

- Improvement in quality of life
- Decreased morbidity and mortality
Treatment of Fabry Disease

Symptomatic Treatment

Treatments Targeting the Underlying Pathophysiology

Germain DP. Orphanet J Rare Dis. 2010;2:5-30
Proteinuria

Proteinuria >1 g/day  0.1-1 g/day  <0.1 g/day

Symptomatic treatment

Proteinuria and Hypertension
ACEI/ARB

Dialysis

Transplantation
# Fabry Disease – Specific Treatment Enzyme Replacement Treatment (ERT)

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<tr>
<th><strong>Agalsidase alpha</strong></th>
<th><strong>Agalsidase beta</strong></th>
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<td>2001</td>
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<tr>
<td>Produced in human fibroblasts</td>
<td>1.0 mg/kg IV every two weeks</td>
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<td>0.2 mg/kg IV every two weeks</td>
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**Enzyme Replacement Treatment (ERT)**

- **Agalsidase alpha**
  - 2001
  - Produced in human fibroblasts
  - 0.2 mg/kg IV every two weeks

- **Agalsidase beta**
  - Produced in Chinese hamster egg cells
  - 1.0 mg/kg IV every two weeks
NIH Trial

26 Affected male pts

Agalsidase alpha (Replagal)
0.2 mg/kg every two weeks 12 doses (24 w)

Placebo

Primary endpoint

Decrease in neuropathic pain
Decrease in plasma and urine Gb3

NIH Trial – Renal involvement

GFR (inulin clearance, 24-h urine protein, Basal and 24. w kidney protocol biopsies)

- Agalsidaz alfa
  - GFR decrease at 24. w: -6.2 mL/min /1.73 m²
  - Mesangial enlargement: -12.5

- Placebo
  - GFR decrease at 24. w: -19.5 mL/min /1.73 m²
  - +16.5

No change in proteinuria
No change in segmental/global sclerosis

NIH Trial – Open label long term– 25/26 pts – 4 years

108 pts (incl. NIH patients)

Annual decrease in GFR

ERT (+)  ERT (-)

Proteinuria >1 g/d*  <1 g/d*

*All ERT (+)

West M, JASN 2009;20:1132
International Fabry Disease Study

58 pts (2 Female)

Agalsidase beta (Fabrazyme)
1 mg/kg
Every two weeks
10 doses (20 w)

Placebo

Primary end-point

Glomerular endothelial
Gb3 deposition 0 vs 69
Cardiac and skin vascular
endothelial cells Gb3
levels

No change in RFT
and pain

Eng JM, et al. NEJM 2001; 5: 9-16
International Fabry Disease Study

6 mo open-label Agalsidaz beta

Disappearance of Gb3 deposition in glomerular endothelial, mesangial and interstitial cells
Mild decrease in Gb3 deposition in podocyte, distal tubular epithelial cells and arterial smooth muscle cells

International Fabry Disease Study – 10 years follow-up

6 mo open-label Agalsidaz beta

Disappearance of Gb3 deposition in glomerular endothelial, mesangial and interstitial cells
Mild decrease in Gb3 deposition in podocytocyte, distal tubular epithelial cells and arterial smooth muscle cells

52 pts RFT stable Decrease in GL3 deposition

58 pts – 4 yr follow-up

58 pts – 10 yr follow-up

No MCE in 81% (42/52) pts
94% (49/52) were alive
10 patients reported 16 events

Annual decrease in eGFR is −1.89 and −6.82 mL/min/1.73 m² in low renal involv. vs high renal involv. (>1.3 g proteinuria, basal GFR 100, 10 yrs late treatment)

Patients who initiated treatment at a younger age and with less kidney involvement benefited the most from therapy. Patients who initiated treatment at older ages and/or had advanced renal disease experienced disease progression.

Pediatric Trials
NIH + 2 centers - 6 month, open label

24 pts (5 Female)
Mean age: 12 yrs

Agalsidase alpha
0.2 mg/kg
Every two weeks, 10 doses (20 weeks)

Decrease in plasma Gb3 (M)
Normal basal eGFR remained stable
Nonsignificant decrease in pain score
Increase in sweating

6 months

3.5 years

Decrease in
- Severity of pain
- Heart rate variab.

Pediatric Trials

16 pts (2 F) (8-16 yrs)

Agalsidase beta
1 mg/kg
Every two weeks (4 months)

4 months

Decrease in dermal capillary Gb3 (13 pts)
Decrease in GI complaints
Better school attendance

Studies in Children
European Fabry Outcome Survey (FOS)

56 centers, 17 country, 98 pts (34 F)

Agalsidase alpha (Fabrazyme)
0.2 mg/kg
Every two weeks (6 months)

No change in RFT and LVMI, remained stable

1-2 years
Not significant reduction in symptomatic patients

Studies in Children
ERT – Long term renal effects

- 12 pts (children and young adult, mean age: 16 yrs)
  - Agalsidase apha or beta
  - Stable RFT
  - Decrease in proteinuria (5/9 pts)

Subjective: Complete disappearance of Gb3 deposition in glomerular endothelial and mesangial cells, partial disappearance in podocytes

5 yrs treatment

No/minimal renal involvement
Basal and 5 years later protocol biopsies

Total ERT dose α Podocyte GB3 decrease
Total ERT dose α Decrease in proteinuria

Tondel, et al JASN 2013
ESKD – ERT in children

- 6 HD pts
- 2 years 1 mg/kg Agalsidase beta tx
  - Slowing LVMI increase
  - Decrease in hot intolerance, GI complaints, abdominal pain, pain killer use, acroparesthesia

RTx – ERT in children

- 3 pts
- 18 mo Agalsidase alpha
  - 3 pts – pain decrease
  - 2 pts – improvement in cardiac morphological abnormalities

Pisani A, AJKD 2005; 46:120
Mignani, KI 2004, NDT 2008
Fabry Disease- ERT Renal Indications

Treatment with ERT is indicated in patients who have any of the following features (it is anticipated that patients may not manifest symptoms or signs in all these areas).

1. **General symptoms of Anderson-Fabry disease, specifically - Uncontrolled pain** leading to a need to alter lifestyle or pain that interferes with quality of life *Pain is often a first manifestation of the disease and therapy started at this stage is also intended to arrest progression to involvement of other organ systems.

2. **Evidence of renal disease**
   a. Clinically significant reduction in Glomerular Filtration Rate (< 80 ml/min)
   b. Proteinuria >300 mgs/24 hours.
   c. Microalbuminuria where a renal biopsy showed endothelial deposits

3. **Evidence of cardiac disease**
   A. ECG a. presence of left ventricular hypertrophy (Romhilt-Estes or Cornell criteria) b. Isolated repolarisation abnormalities (in absence of other causes such as hypertension, aortic stenosis) c. Conduction abnormalities: (Short PR interval, 1, 2 or 3 degree heart block, bundle branch block) B. Echocardiogram a. Increased left ventricular mass (in patients with concentric remodelling or hypertrophy) Criteria (Devereux et al 1977,1986) Normal LVMI defined as < 134 gm/m2 for men and < 110 gm/m2 in females. Relative wall thickness (RWT) calculated as ((IVS + PW)/LVed) at the mitral valve level. LV remodelling or LVH defined as a RWT > 0.4514. LV geometry defined as normal (normal LV mass and normal RWT), concentric remodelling (normal LV mass and increased RWT), eccentric LVH (increased LV mass and normal RWT), and concentric LVH (increased LV mass and increased RWT). b. Increased left ventricular wall thickness (13 mm in any segment). c. Left atrial enlargement d. Valvular thickening/insufficiency e. Systolic impairment (regional wall motion abnormality or reduction in left ventricular ejection fraction (< 50%)
   f. Diastolic dysfunction (using age corrected Doppler assessment )
   C. Arrhythmia a. 24 hour ECG (or other documented ECG evidence) showing bradyarrhythmia, atrial arrhythmia, ventricular tachycardia.
   D. Ischaemic heart disease: positive exercise test, PET scan in the ABSENCE of angiographically significant epicardial coronary artery disease.

4. **Evidence of Neurovascular disease**
   - Previous stroke or TIA in the absence of other risk factors - Progression of abnormal cerebral MRI scans

5. **Gastrointestinal symptoms such as pain, vomiting or altered bowel habit** which are significantly reducing quality of life and not attributable to other pathology.

6. **Episodic vertigo interfering with quality of life**

7. **Hearing loss**
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<th>Age Group</th>
<th>Recommended Action</th>
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<td>&gt;16 yrs, male</td>
<td>At diagnosis</td>
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<td>&lt;16 yrs, males</td>
<td>Symptomatic age</td>
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<td>Asymptomatic, 10-13 yrs</td>
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<tr>
<td>Females (all ages)</td>
<td>Follow-up is very important</td>
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<td>Symptomatic disease or progressive organ involvement</td>
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</table>

*Eng C et al, 2006*
ERBP Guideline – Who should receive ERT?

- Affected males
- Symptomatic females

ERBP Guideline – ERT – Renal conditions

- GFR < 60 mL/min/1.73 m²
- Proteinuria >1 g/d
- After renal transplantation

- ACEI
- 25 (OH) vitamin D ---- KDIGO recommendation

ERBP, 2013 NDT
ERBP Recommendations

• Newborn screening is not recommended

• Female carriers are not recommended as donors

• In exceptional cases, biopsy should be performed before
Cochrane review

- 6 eligible studies (223 pts)
  - 2 studies Agalsidase alpha vs placebo
  - 3 studies Agalsidase beta vs placebo
  - 1 study Agalsidase alpha vs Agalsidase beta
- Not enough evidence for ERT

31 studies
- 6 studies included meta-analysis
- ERT efficiency was evaluated in different disease stages
- Main clinical outcomes
  - Renal function
  - Left ventricular mass index
  - White matter lesions in brain
  - Target organ complications
The European Fabry Working Group (EFWG) Recommendations - 2015

• For **classically affected males**, ERT is recommended as soon as there are early clinical signs of kidney, heart or brain involvement, but may be considered in patients of ≥16 years in the absence of clinical signs or symptoms of organ involvement.

• **Classically affected females** and **males with non-classical FD** should be treated as soon as there are early clinical signs of kidney, heart or brain involvement, while treatment may be considered in females with non-classical FD with early clinical signs that are considered to be due to FD.
The European Fabry Working Group (EFWG) Recommendations - 2015

- Treatment should not be withheld from patients with severe renal insufficiency (GFR < 45 ml/min/1.73 m$^2$) and from those on dialysis or with cognitive decline, but carefully considered on an individual basis.

- Stopping ERT may be considered in patients with end stage FD or other co-morbidities, leading to a life expectancy of <1 year.

- In those with cognitive decline of any cause, or lack of response for 1 year when the sole indication for ERT is neuropathic pain, stopping ERT may be considered.

- Also, in patients with ESKD, without an option for renal Tx, in combination with advanced heart failure (NYHA class IV), cessation of ERT should be considered.

- ERT in patients who are non-compliant or fail to attend regularly at visits should be stopped.
Final Conclusion

- Life expectancy in Fabry disease is 20 years shorter in males and 10-15 years in females.
- ESKD is the second most common reason of death.
- Careful follow-up with a multidisciplinary team is important.
- In correct indications, disease morbidity can be prevented by early ERT.
Oral Pharmacological Chaperone Migalastat (Galafold) Therapy for Fabry Disease

- Migalastat is not immunogenic
- Oral administration: No infusion-associated reactions or infections, no pre-infusion medications would be needed
- Large volume of distribution
  - including access across the blood-brain barrier in mice
- Every other day oral migalastat was shown in trials to lead to consistent increases in alpha Gal A closely mimicking natural enzyme trafficking

Johnson et al, 2013, Clin Pharm in Drug Development; Bichet et al, 2016, WORLD; F.Johnson et al, 2016, WORLD; Khanna et al 2010; Molecular Therapy
Decreased substrate accumulation
PHARMACOLOGICAL CHAPERON

MUTATION

Endoplasmic reticulum

Decreased substrate accumulation

Lysosome
- 28 days of oral administration of migalastat
- Significant increases in α-Gal A activity and reductions in GL-3 observed in disease-relevant tissues
- Investigation of dose-response and administration frequency in this model support QOD administration at 150 mg in humans

Khanna R, et al, 2010, Molecular Therapy
The Rate of Change in eGFR is Comparable To Rates Reported in the Literature for Subjects on ERT

Preliminary Data

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N, yrs</td>
<td>n=14, 4 yrs</td>
<td>n=20, 1 yr</td>
<td>n=54, 0.5 yrs</td>
<td>N=117, 8.5 yrs</td>
<td>n=10, 4.3 yrs</td>
<td>n=6, 1.5 yrs</td>
<td>n=22, 3.0 yrs</td>
<td>n=42, 1.9 yrs</td>
<td>n=9, 1.9 yrs</td>
<td>n=58, 2.1 yrs</td>
<td>n=16, 2.9 yrs</td>
<td>n=12, 3.0 yrs</td>
<td>n=58, 2.1 yrs</td>
<td>n=16, 2.9 yrs</td>
<td>n=12, 3.0 yrs</td>
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<td>Treatment</td>
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<td>none</td>
<td>none</td>
<td>none</td>
<td>FAB</td>
<td>FAB</td>
<td>REP</td>
<td>FAB</td>
<td>FAB</td>
<td>REP</td>
<td>FAB</td>
<td>REP</td>
<td>FAB</td>
<td>Amigal Ph2, ALL</td>
<td>Amigal Ph2, R*</td>
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<tr>
<td># With Baseline Proteinuria ≥ 1g</td>
<td>N/A</td>
<td>4/20 (e)</td>
<td>N/A</td>
<td>N/A***</td>
<td>0/42</td>
<td>0/9</td>
<td>0/58</td>
<td>1/16</td>
<td>1/12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BL GFR</td>
<td>CRI onset</td>
<td>70</td>
<td>85</td>
<td>≥60</td>
<td>~100</td>
<td>79</td>
<td>90**</td>
<td>~135</td>
<td>94</td>
<td>90**</td>
<td>91</td>
<td>91</td>
<td>91</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: Figure modified from West, 2009; West, Breunig and AT1001 data exclude hyperfiltrators (>135 ml/min); *GR=good responders, ** mean GFR for all subjects in West 2009 prior to ERT was 90 ml/min, *** 19/117 subjects in Schiffmann 2009 had 24-hr protein > 0.3g

Germain PD et al. Orphanet J Rare Dis 2012 Nov24, 7:91
Conclusion – 1
When to Suspect Fabry Disease

- Any patient with multi-system symptoms that vary in age of onset, severity and manner of progression
- Angina, dyspnea or stroke in young adults with no cardiovascular risk factors
- Unexplained, early-onset kidney disease (including cysts, proteinuria, reduced renal function)
- Unexplained syncope
- Ocular symptoms and signs of corneal deposits
- Frequent GI symptoms during childhood and/or adolescence
- History of pain through adolescence (‘growing pains’ ?)
- Hypertension in young adults associated with long-lasting, non-specific symptoms such as depression and pain attacks
- Family history of cryptogenic stroke and/or TIA

Conclusion -2
The Multidisciplinary Approach To Fabry Disease

CLINICAL SERVICES
- Cardiology
- Dermatology
- Endocrinology
- Gastroenterology
- Nephrology
- Neurology
- Ophthalmology
- Orthopaedics
- Otolaryngology/audiology
- Pain management
- Psychology
- Pulmonology
- Physiotherapy

DIAGNOSTIC SERVICES
- Biochemistry
- Genetics
- Haematology
- Radiology
- Nuclear Medicine
- Pathology

SUPPORT SERVICES
- Pharmacy facilities
- Administrative support
- Social services
- Financial advice
- Patient support

Lead Consultant

Biomarkers in Fabry Disease-2

- **Urinary or plasma Gb3 (Globotriaosylceramide) (the main substrate)**
  - Elevated in both males and females in 24 hr urine collection
  - Marked variability in children from birth to 6 m
  - Can be a marker for treatment but does not have clinical correlation.
  - Does not have a prognostic significance.
  - Urine is said to be better

- **Urinary or plasma Globotriaosylsphingosine or lyso-Gb3**
  (deacylated Globotriaosylceramide)
  - Statistically high levels in classical FD, better marker than Gb3
  - Elevated in hemizygous males, lesser in adult females with classical Fabry.
  - Elevated at baseline and to fall more dramatically on ERT than that of Gb3
  - Not suitable for NBS

- **Others¹**
  - Sphingosine-1-phosphate (S1P)
  - N-Terminal Pro-Brain Natriuretic Peptide
  - Vascular Endothelial Growth Factor (VEGF-A)

---


Johannes M. F. G. Aerts, J Inherit Metab Dis (2011) 34:605–619
2 Johnson B et al., Ann Lab Med 2013;33:274-278
Fabry Disease in Female and Male Patients: Clinical Differences

- Despite X-linked inheritance, females may develop severe signs and symptoms
- In females, α-galactosidase A activity may be normal, DNA testing must be used to confirm diagnosis
- Of the 1077 females in Fabry Registry % 69.4 had signs or symptoms
- Major organ involvement occurred about a decade later than the males
  - There is higher frequency of cerebrovascular events in females
  - Cardiac involvement is more severe and renal events are more common in males

Renal Involvement in Fabry Disease is Classified as ‘Classic’ or ‘Variant’

• The predominant signs of ‘classic’ renal involvement are:
  – Glomerular damage and glomerulosclerosis
  – Proteinuria, microalbuminuria and haematuria
  – Renal cysts
  – Progressive decline in GFR
  – Dialysis or renal transplant in the second or third decade of life in males
  – ESRD, generally in the fourth of fifth decade of life in males

• Renal ‘variant’ patients do not exhibit many of the ‘classic’ signs:
  – Disease manifestations are confined to the kidney
  – Late-onset proteinuria and ESRD, typically after 50 years of age
  – Detected in 0.24–1.00% of males in haemodialysis

Misdiagnosis of familial Mediterranean fever in patients with Anderson-Fabry disease

Study
- MEFV and GLA mutations investigated in 42 unrelated patients with a clinical diagnosis of FMF

Result
- MEFV Sequencing
  - 7/42 homozygous mutation (16.7%)
  - 3/42 compound heterozygotes (7.1%)
  - 20/42 single mutation (47.6%)
  - 12/42 (28.6%) no mutation

- GLA sequencing
  - 3/42 mutation (7.14%)
  - 2 of these also carried a single mutation on the MEFV gene
  - Family screening of these three revealed 8 additional cases

FMF, familial Mediterranean fever.
Kidney Involvement-2

Renal capillary endothelium filled with glycosphingolipids (LM)

Atrophic and hyalinized glomeruli in kidney biopsy (LM)
2012 Canadian Fabry Disease Treatment Guidelines

• Major criteria:
  Fabry nephropathy with reduced GFR
  Persisting proteinuria of ≥500 mL/day/1.73m² with no other cause

• Minor criteria:
  Hyperfiltration
  Isolated proteinuria of ≥300 mL/day/1.73m² with no other cause
  Renal tubular dysfunction
  Hypertension
  Renal pathology (not mandatory, but may be considered if a renal biopsy is performed)

• Other possible causes of nephropathy should first be excluded

one major or two minor criteria
Recommendations for Screening for Fabry in Patients with ESRD

ERBP Consensus Report

• Screening for FD in male CKD patients below 50 years of age in whom a reliable renal diagnosis is absent.

• Screening for FD in females with unexplained CKD, irrespective of age, with other unexplained symptoms potentially associated with FD.

• Using enzyme activity measurement for alpha-Gal A as a primary tool in males, followed by confirmation with mutation analysis when positive.

• Using mutation analysis as a primary tool for screening in females.

CKD, chronic kidney disease; ESRD, end-stage renal disease; FD, Fabry disease.
International Fabry Registry

Clinical event
Cardiac (MI, important intervention, arrhythmia, angina, CHF)
Central (CVA)
Renal (chronic dialysis, renal transplant or eGFR < 10 ml/dk/1.73 m²)
Death

Clinical event
Cardiac (MI, important intervention, arrhythmia, angina, CHF)
Central (CVA)
Renal (chronic dialysis, renal transplant or eGFR < 10 ml/dk/1.73 m²)
Death

Outcomes of patients treated through the Canadian Fabry disease initiative

S.M. Sirrs a,*, D.G. Bichet b, R. Casey c, J.T.R. Clarke d, K. Lemoine e, S. Doucette f, M.L. West g,
On behalf of the CFDI investigators

a Department of Medicine University of British Columbia, Canada
b Department of Medicine University of Montreal, Canada
c Department of Pediatrics University of Calgary, Canada
d Department of Pediatrics, Hospital for Sick Children and Centre Hospitalier Universitaire de Sherbrooke, Canada
e Department of Pediatrics, Capital District Health Authority, Canada
f Department of Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada
g Department of Medicine Dalhousie University, Canada

362 pts, 5 y follow-up, composite end point
- Death
- Neurological event
- Cardiovascular event
- ESKD or %0% increase in basal creatinine

Group 1a: Pts on ERT
Group 1b: Pts not on ERT (can be started during follow-up)
Group 1c: Patients without ERT
Total number of patients on ERT: 178

Renal, CVS, CNS, GI, pain
BP<130/80 mmHg
LDL in normal limits
ACEI
Aspirin
Statin
CV risk modification
Central follow-up
Close follow-up
Correct indications for ERT use

Decrease
in CV events,
in tenal events and
in deaths
No effect on stroke
### Analysis 1.7. Comparison 1 Agalsidase alfa versus placebo, Outcome 7 Creatinine clearance.

Review: Enzyme replacement therapy for Anderson-Fabry disease

Comparison: 1 Agalsidase alfa versus placebo

Outcome: 7 Creatinine clearance

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Agalsidase-alfa</th>
<th>Placebo</th>
<th>Mean Difference</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
</tr>
<tr>
<td>At up to 6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiffmann 2001</td>
<td>13</td>
<td>94.8 (27.76)</td>
<td>11</td>
</tr>
</tbody>
</table>

### Analysis 2.3. Comparison 2 Agalsidase beta versus placebo, Outcome 3 Renal events (intention-to-treat population).

Review: Enzyme replacement therapy for Anderson-Fabry disease

Comparison: 2 Agalsidase beta versus placebo

Outcome: 3 Renal events (intention-to-treat population)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Agalsidase beta</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Bankazemi 2007</td>
<td>10/51</td>
<td>7/31</td>
<td>0.87 [ 0.37, 2.04 ]</td>
</tr>
</tbody>
</table>
### Analysis 2.2. Comparison 2 Agalsidase beta versus placebo, Outcome 2 Death (intention-to-treat population).

Review:  Enzyme replacement therapy for Anderson-Fabry disease  
Comparison:  2. Agalsidase beta versus placebo  
Outcome:  2 Death (intention-to-treat population)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Agalsidase beta</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Banikazemi 2007</td>
<td>1/51</td>
<td>0/31</td>
<td>1.85 [0.08, 43.96]</td>
</tr>
</tbody>
</table>

### Analysis 2.6. Comparison 2 Agalsidase beta versus placebo, Outcome 6 Cardiac events.

Review:  Enzyme replacement therapy for Anderson-Fabry disease  
Comparison:  2. Agalsidase beta versus placebo  
Outcome:  6 Cardiac events

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Agalsidase beta</th>
<th>Placebo</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H, Fixed, 95% CI</td>
<td>100.0 %</td>
<td>0.46 [0.11, 1.90]</td>
</tr>
<tr>
<td>Banikazemi 2007</td>
<td>3/51</td>
<td>4/31</td>
<td>100.0 %</td>
<td>0.46 [0.11, 1.90]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>51</td>
<td>31</td>
<td>100.0 %</td>
<td>0.46 [0.11, 1.90]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 3 (Agalsidase beta), 4 (Placebo)  
Heterogeneity: not applicable  
Test for overall effect: Z = 1.08 (P = 0.28)  
Test for subgroup differences: Not applicable
# Guidelines for Follow-Up of Patients With Fabry Disease

<table>
<thead>
<tr>
<th>System</th>
<th>Assessment</th>
<th>Guidelines</th>
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</thead>
<tbody>
<tr>
<td>General</td>
<td>General status, quality of life (SF36® Health survey, EuroQOL or PedsQL® measurement mode), school or work performance, depression, anxiety, drug use, somatic growth</td>
<td>Baseline (at first visit), every 12 months</td>
</tr>
<tr>
<td></td>
<td>Complete physical examination</td>
<td>Baseline, every 12 months</td>
</tr>
<tr>
<td></td>
<td>Genetic counseling</td>
<td>Baseline, on request</td>
</tr>
<tr>
<td></td>
<td>Alpha-galactosidase A activity and genotype</td>
<td>If not previously performed or determined</td>
</tr>
<tr>
<td>Kidney</td>
<td>Serum creatinine, ionogram, BUN; morning spot urine for urinary protein/creatinine ratio and albumin/creatinine ratio</td>
<td>Baseline. Every 3 months if CKD stage 1 or 2 and &gt;1 g/day of proteinuria or CKD stage 4 Every 6 months if CKD stage 3 Every 12 months if CKD stage 1 or 2 and &lt;1 g/ day of proteinuria</td>
</tr>
<tr>
<td></td>
<td>Urinary Gb3 (optional)</td>
<td></td>
</tr>
</tbody>
</table>

Chronic kidney disease (CKD) stages: 1. Glomerular filtration rate (GFR) >90 mL/min/1.73 m²; 2. GFR >60 to <89 mL/min/1.73 m²; 3. GFR >30 to <59 mL/min/1.73 m²; 4. GFR >15 to <29 mL/min/1.73 m²; 5. GFR <15 mL/min/1.73 m² or end stage renal disease (ESRD) (dialysis or transplantation)

1. Eng CM et al., Genet Med. 2006;8:539-48. 2. Germain DP. Orphanet J Rare Dis. 2010;2;5-30
Long-term enzyme replacement therapy is associated with reduced proteinuria and preserved proximal tubular function in women with Fabry disease

Thanea Prabakaran, Henrik Birk, Bo M. Bibby, Axel Regeniter, Søren S. Sørensen, Ulla Feldt-Rasmussen, Rikke Nielsen and Erik I. Christensen

1Department of Biomedicine, Aarhus University, Aarhus, Denmark; 2Department of Nephrology, Aarhus University Hospital, Aarhus, Denmark; 3Department of Biostatistics, Aarhus University, Aarhus, Denmark; 4Laboratory Medicine, Basel University Hospital, Basel, Switzerland; 5Department P. Righospital, Copenhagen, Denmark and 6Department of Medical Endocrinology, Righospital, Copenhagen, Denmark

13 female patients
Mild nephropathy
Agalsidase beta
Mean age: 45 y
Urine alb/Cr: 1
Follow-up: 6 y

4 female patients
No treatment
Mean age: 34 y
Urine alb/Cr: 0.26
Follow-up: 5 y
Progression of Nephropathy in Males and Females

- Estimated GFR regression slopes in male and female patients with Fabry disease with and without ESRD

- Non-ESRD males: GFR slope = -2.93
- Non-ESRD females: GFR slope = -1.02
- ESRD males: GFR slope = -3.85
- ESRD females: GFR slope = -3.05

Schiffman, NDT 2009; Mehta Eur J Clin Invest 2004
Renal Failure as a Leading Cause of Mortality from Fabry Disease

Cardiac deaths are 3-4X higher than renal deaths

FOS* (n=1453, as of December 2007)¹

- 42 deceased patients
- Renal disease accounted for 3 deaths (all males)
- Cardiac disease was the most frequent cause of death (12 male, 4 female)

- 87 deceased patients; cause of death known in 66 (56 male, 10 female)
- Renal disease accounted for 7 deaths (6 male, 1 female)
- Cardiac disease was the most frequent cause of death (30 male, 5 female); 60% of these patients (19 male, 2 female) had previously experienced a renal event

Affected relatives of patients enrolled in FOS (n=181 as of December 2007)¹

- 181 deceased patients, most of whom died before 2001
- Renal disease was the most frequent cause of death (50 male, 7 female)

Weekly Agalsidase alpha in 11 pts with a continued decline in renal function despite therapy

International Fabry Disease Study- 4 years follow-up

6 mo open label Agalsidase beta

6 pts – renal progression
- > 2 g proteinuria
- > 40 yr
- > 50% crescent

52 pts RFT stable
Decrease in GL3 deposition

58 pts – 4 yr follow-up

Disappearance of Gb3 deposition in glomerular endothelial, mesangial and interstitial cells
Mild decrease in Gb3 deposition in podocyte, distal tubular epithelial cells and arterial smooth muscle cells

Germain DP, et al. JASN 2007; 18:1547-
Fabry Disease Clinical Trial Study Group

Multicenter
82 pts
Mild-moderate renal involvement
GFR: 53 ml/dk71.73 m²
Proteinuria: 1.3 g/d

Primary endpoint – Major clinical event
Renal (ESKD – 33% increase in Cre)
Cardiac (MI, arrhythmia, angina)
Neurologic (CVA, TIA)
Death

Proteinuria is more prominent in Agalsidase pts
No significant decrease in MCEs in proteinuric pts
Agalsidase is beneficial in compliant patients
Partial benefit in pts with GFR > 55 ml/dk71.73 m²