PAEDIATRIC MANAGEMENT

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Disclosure of Interests

UR has received travel grants and lecture fees from Shire HGT, Amicus and Genzyme; and advisory board consultancy fees from Shire HGT and Amicus.

Outline

- Unmet Need
- Late complications in Fabry Disease
- Microalbuminuria – pitfalls
- Early biomarkers of renal function
  - Glomerular
  - Tubular
- Conclusion

UNMET NEED

Early non-invasive Biomarkers of Glomerular and Tubular Damage alleviating the need for frequent renal biopsies in early childhood

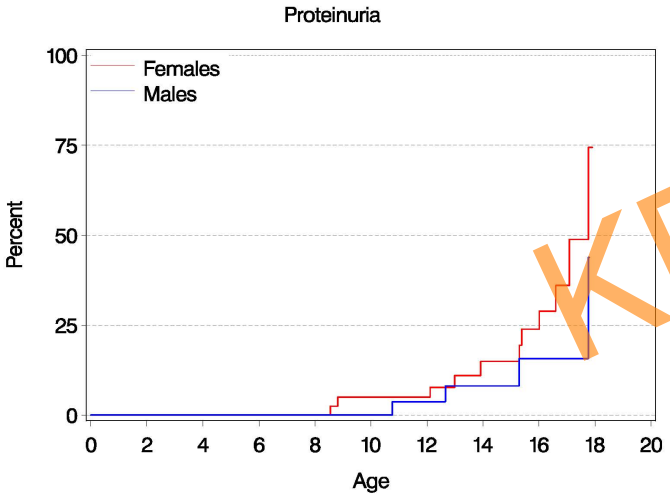
Fabry Disease UK Guidelines: Paediatric Baseline Assessment at Diagnosis; follow up and commencement of therapy

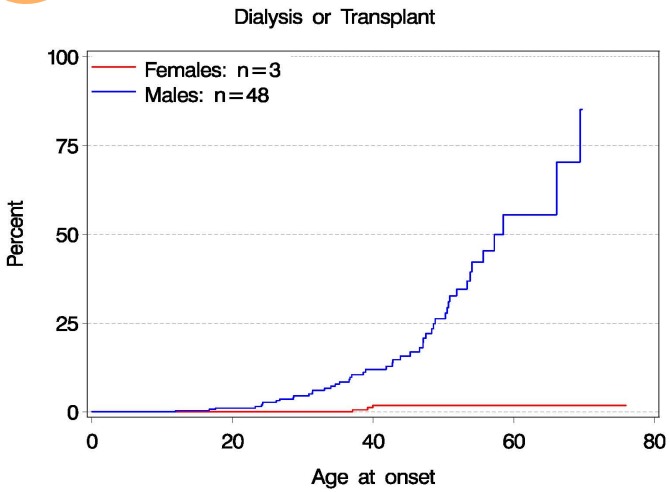
Renal:

- Twenty Four Hour urine protein – when potty trained and co-operative
- Spot urine Alb:Cr ratio; protein: creatinine ratio x 3 consec early morning urine
- Urine CTH (10 mls of urine in a universal container sent either immediately or frozen as for blood).
- Glomerular Filtration Rate: Cr51 EDTA –

  Once every 2 to 3 years: Over 5 years of age in boys and 10 years of age in girls. eGFR using CB/Schwartz methods annually
- Renal biopsy- if clinically indicated only (for example: persistent unexplained haematuria and/or persistent nephrotic range proteinuria).

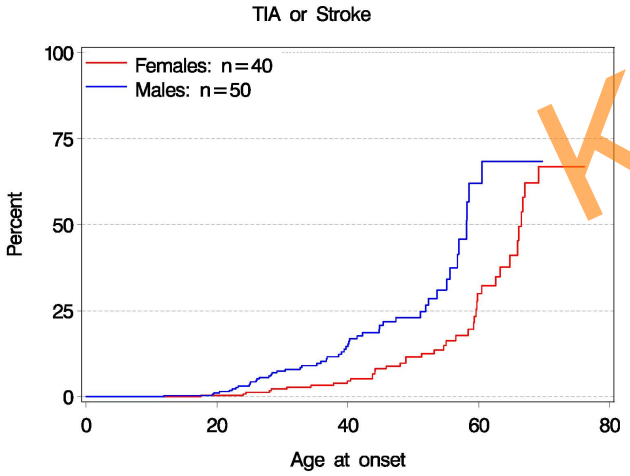
Late complications of FD rare in Childhood

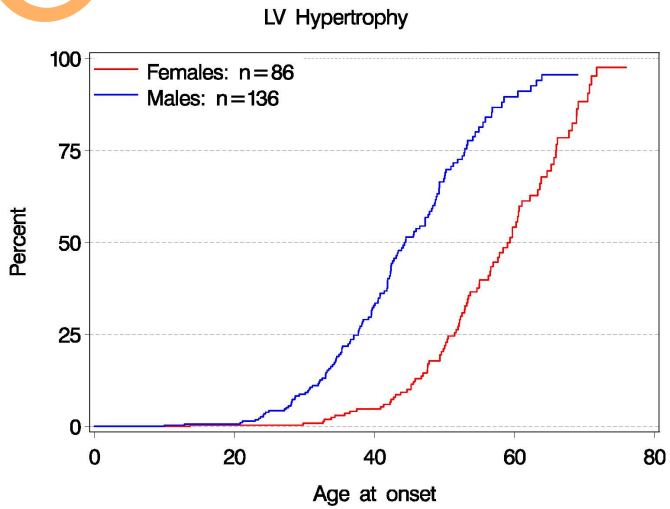




Fabry Outcome Survey 2005

Late complications of FD rare in Childhood





Fabry Outcome Survey 2005

Proteinuria in Fabry Disease

Proteinuria is of glomerular origin in almost all cases, albumin representing its major component (≥50%) in adults but only 10-15% in childhood.

The prevalence of proteinuria increases with age, being relatively uncommon in children and teenagers.

By the age of 35 years, 50% of affected males are estimated to have proteinuria

All patients who survive into the 6th decade of life eventually develop proteinuria.

Nephrotic range proteinuria occurs in <20% of male Fabry patients with CKD, but full blown presentation of nephrotic syndrome is relatively unusual.

Death from ESRD on the 4th or early on the 5th decade of life was a frequent outcome in untreated males.

ERT/ Adjunctive renal therapies has increased the median age of death by more than a decade.

Urine Albumin Excretion (UAE) Rate

- In both normal and diabetic patients UAE is higher during the day than during the night.
- It is increased by strenuous exercise, fluid or salt loading, oral protein challenge, hyperglycaemia and other factors causing the increase of intra-glomerular pressure.
- A day-to-day biological variation of UAER is about 40%.
- Orthostatic proteinuria a common phenomena, emphasising the importance of early morning urine samples.
- It is therefore generally agreed that to make a diagnosis of microalbuminuria, UAER should be in the microalbuminuric range in at least two out of three collections over a time period of 3 months

Cohen D.L Diabetic Med. 1987, 4, 437.

Pitfalls with Albumin/Creatinine measurements

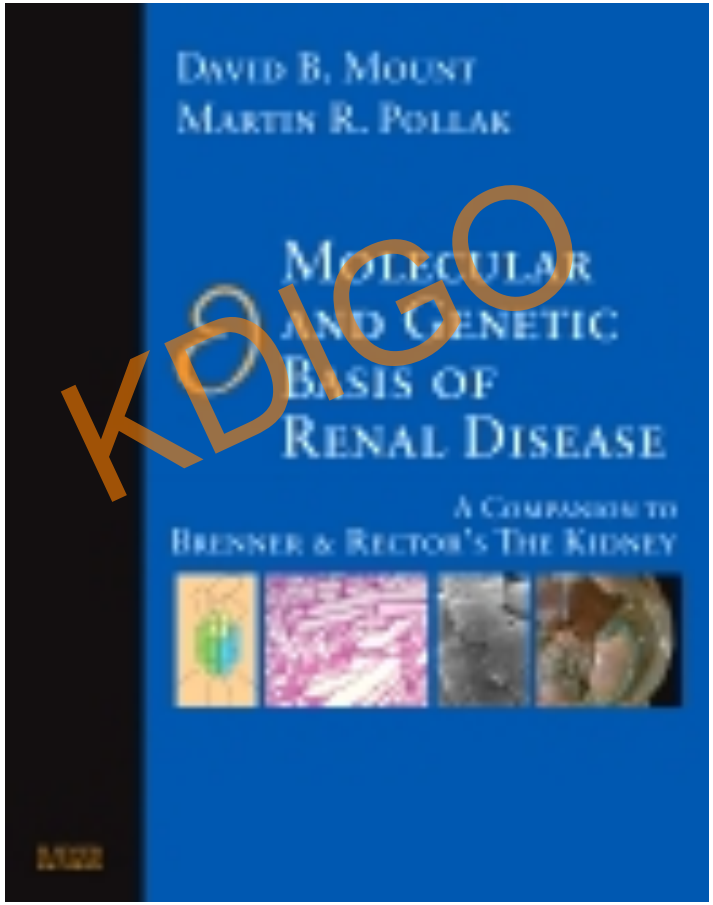
- Not all centres able to collect three consecutive samples
- Routine RIA methodology does not measure non-immunoreactive albumin and hence may result in false negative results
- Albumin excretion rate is a continuous variable.
- But: If three consecutive values are elevated above the normal range this reflects increased nephropathy risk.

Early podocytopathy in paediatric Fabry disease in the absence of microalbuminuria

Am J Kidney Dis. 2008 May;51(5):767-76. doi: 10.1053/j.ajkd.2007.12.032. Epub 2008 Mar 20.
Renal biopsy findings in children and adolescents with Fabry disease and minimal albuminuria.
Tøndel C1, Bostad L, Hirth A, Svarstad E.

J Am Soc Nephrol. 2013 Jan;24(1):137-48. doi: 10.1681/ASN.2012030316.
Agalsidase benefits renal histology in young patients with Fabry disease.
Tøndel C1, Bostad L, Larsen KK, Hirth A, Vikse BE, Houge G, Svarstad E.

Clin J Am Soc Nephrol 7: 1591–1597, 2012. doi: 10.2215/CJN.02150212
Safety and Complications of Percutaneous Kidney Biopsies in 715 Children and 8573 Adults in Norway 1988–2010.
Camilla Tøndel, Bjørn Egil Vikse, Leif Bostad, and Einar Svarstad


David B. Mount
Martin R. Pollak
Molecular and Genetic Basis of Renal Disease
A Companion to Brenner & Rector's The Kidney

Podcytopathies

Clinical Disorder	Gene	Locus	Inheritance	Gene Product	Age of onset	OMIM
Slit Diaphram and podocyte associated disease						
Congenital Nephrotic Syndrome (Finnish)	NPHS1	19q13.1	AR	NEPHRIN	Infancy	256300
Steroid Resistant NS/FSGS	NPHS2	1q25.3	AR	podocin	3 months to adulthood	600995
FSGS	CD2AP	6p12	AD	CD2AP	Adult	604241
FSGS	TRPC6	11q21-22	AD	TRPC6	Adult	603965
FSGS	ACTN4	19q13	AD	Alphaactinin4	Late	603278
Syndromic podocyte disorders						
Denys Drash	WT1	11p13	AD	WT1	Infancy	194080
Nail Patella	LMX1B	9q34	AD	LMX1B	late	161200
Pierson	LAMB2	3p2.1	AR	Lamn-beta2 chain	infancy	609049
Fabry disease	GLA	Xq22	x-linked	Alpha gal A	Adulthood	301500
Immuno-osseous dysplasia	SMARCAL 2	2q34-36	AR	SMARCA like protein 1	childhood	242900
CD151 deficiency	CD151	11p15	AR	CD151	adolescence	609057

Biomarkers of podocyte injury

Indicators of podocyte injury:

Nephrin, podocin, podocalyxin, CR1, CD80, synaptopodin, GLEPP-1, mindin, alpha 3 integrin, CD59, and WT1 protein.

These proteins can be detected by various methods like immunofluorescent staining, western blot, enzyme-linked immunosorbent assay (ELISA), flow cytometry, and mass spectrometry.

Sekulic M, Pichler Sekulic S. A Compendium of Urinary Biomarkers Indicative of Glomerular Podocytopathy. Patholog Res Int. 2013;2013:782395

Alternative early biomarkers of glomerular disease: Urine Nephrin/podocin/podocalyxin

- Currently, urine microalbuminuria is used as an early indicator of glomerular injury.
- Both animal and human studies have demonstrated that nephrinuria occurs early in glomerular injury, preceding albuminuria, and that there is a positive correlation with severity of renal diseases.
- Urine nephrin analysis thus has the potential to become an important biomarker of early glomerular injury.
- To date, no studies on children or adolescents have been published, pointing to a need for clinical studies using urinary nephrin to assess, monitor, and prognosticate renal diseases in children.

Sekulic M et al 2013

Early Markers of Tubulopathy

- Electron microscopy in Fabry Disease: Electron-dense multi-lamellar membranous inclusions within phagolysosomes and within lysosomes of tubular cells: **GSL accumulates probably in lysosomes of renal tubular cells.**

- Heterozygote individuals had similar distribution but less quantity of cytoplasmic GSL.

- These cells are exfoliated and can be identified specifically in voided urine specimens.

- Examination of renal tubular cells in urine using a fluorescein antibody technique affords a noninvasive means of diagnosing and following the effect of therapy in patients with Fabry disease.

Chatterjee et al, 1984

Early Markers of Tubulopathy

- **Urinary NAG** (N-acetyl-β-D-glucosaminidase) originates primarily from the proximal tubule, and increased urinary excretion is a consequence of renal tubular cell breakdown.

- Urinary concentration of NAG is therefore a sensitive index of renal tubular function.

- **Liver Fatty Acid Binding Protein (L-FABP)** is a small, ~14kDa, highly conserved cytoplasmic protein expressed in the renal proximal tubule where it mediates transport of long chain fatty acids to the mitochondria or peroxisome for ß-oxidation. Due to its small size L-FABP leaks easily out of necrotic cells leading to a rapid rise in urinary levels.

- Increase in serum levels and urinary excretion of neutrophil-gelatinase associated lipocalin (respectively **sNGAL and uNGAL**) and urinary excretion of Cathepsin L (**uCathL**) have been described in children with diabetes, with normoalbuminuria and good metabolic control**: early tubular dysfunction biomarkers**

Sołtysiak et al 2014

Conclusions

- Fabry Nephropathy is slowly progressive
- Glomerular and tubular changes in renal biopsies have been noted in young children without microalbuminuria but with some early neuropathic clinical manifestations
- Renal Biopsy is a valuable tool in the management of Fabry Disease but not practical in the day to day routine management of patients with Fabry Disease in all countries.
- Alternative early biomarkers of glomerular and tubular disease may be important.
- Nephrin has been used in Diabetes as an early biomarker and further studies in children is necessary.
- Tubular dysfunction is often ignored in children with Fabry Disease and should be considered in routine clinical care.