Nephrotic syndrome in children

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What is Nephrotic syndrome??

- Nephrotic syndrome is caused by renal diseases that increase the permeability across the glomerular filtration barrier.
  - Nephrotic range proteinuria — Urinary protein excretion greater than 50 mg/kg per day
  - Hypoalbuminemia — Serum albumin concentration less than 3 g/dL (30 g/L)
  - Edema
  - Hyperlipidemia
Why Nephrotic syndrome

• Nephrotic syndrome is the commonest diagnosis in the pediatric renal clinics at tertiary centres
• Also one of the commonest reason for pediatric nephrology consultation in the wards after acute kidney injury
• most guidelines on nephrotic syndrome renal biopsy based on studies done long ago, in continents far away from here and in populations different from ours
• Local data is scanty at best
• And thus..............
Classification

1. Age of onset
2. Aetiology
3. Histological
4. Response to steroids
Congenital & early onset nephrotic syndrome

- **Congenital** – presentation < 1 month
  (most commonly CNS of Finnish type)

- **Early onset** – can be from days to months
  (Heterogeneous group – diffuse mesangial sclerosis, MCNS)
Classification of congenital and early-onset nephrotic syndrome

Primary NS

- Congenital nephrosis of the Finnish type
- Isolated diffuse mesangial sclerosis
- Denys-Drash syndrome
- Congenital NS with brain and other malformations (Galloway – Mowat syndrome)
- FSGS
- Membranous glomerulosclerosis
Aetiological classification (early or late onset)

- Primary

- Secondary
  - Infections
    - Congenital syphilis
    - Toxoplasmosis, rubella, CMV, Hepatitis, HIV
    - Malaria
  - SLE
Histological classification

Four defined categories of primary podocytopathy:

1. Normal histology – minimal change nephropathy
2. Mesangial sclerosis – diffuse mesangial sclerosis
3. Segmental sclerosis – focal segmental glomerulosclerosis
4.Collapse of the glomerular basement membrane – collapsing glomerulopathy

Schnaper and colleagues
Response to steroids

- Idiopathic NS has an estimated incidence of 20-30 per million children annually
- Of all treated patients
  - 1/3rd - no relapses
  - 1/3rd - infrequent relapses
  - 1/3rd - steroid dependent
  - 7% - steroid resistant – renal biopsy
- 93% steroid-responsive
  - Long-term outcome is excellent
  - Mortality (1%) mostly due to sepsis and thrombosis rather than renal failure
Etiology ??????
Renal biopsy findings in children at Kenyatta National Hospital
Histopathology

- FSGS: 57%
- Mesangiopro: 16%
- mesangiocapillary: 7%
- minimal change: 3%
- crescentic: 12%
- other: 0%
Histopathology

- ISKDC biopsies on 521 children in Europe, N America and Asia showed most children had minimal change (77%) FSGS (2%)
- South Nigeria in children with steroid resistance showed mesangiocapillary 43.5% FSGS 39.1% minimal change 4% (n=  
- Study from Tunisia showed FSGS 50%mesangial proliferation 40%
- American canadian studies showing increasing incidence of FSGS


Tunis Med:2011 Mar;89(3):258-61

Renal Biopsy Review
1990 – 1999 Cape town

• *Mesangial Proliferation  36/96(37.5%)
• FSGS          9/96(9.4%)
• Mesangiocapillary  4/96(4.2%)
• Membranous      19/96(2.1%)
• **Minimal Change Disease**  2/96(2.1%)
Patient

- 7 year old girl first presentation
- Swelling of face and body – ascites +++
- Urine: protein 4+ Blood 2+
- BP 90/60 mmhg
- No impetigo or throat infections
- Clinically cool peripheries, HR 130b/min
  apex not displaced, HS normal

Chest Dull Left base
Clinical manifestations

- Pedal periorbital edema
- Ascites and pleural effusions.
- Infections like peritonitis. (may present as acute abdomen).
- The likelihood of hypertension varies with the underlying cause of nephrotic syndrome.
  - Hypertension is common in patients with focal segmental glomerulosclerosis or glomerulonephritis, but is infrequent in MCD.
- Gross hematuria is most often seen in patients with glomerulonephritis.
Complications

• Infection — Children with nephrotic syndrome have increased susceptibility to encapsulated bacterial infection, particularly peritonitis because of defects in humoral immunity.
  • Although antibiotics have reduced the mortality rate of nephrotic syndrome due to infection, infection still remains the main cause of death in children with nephrotic syndrome.

• Anasarca — Anasarca (generalized and massive edema) can cause
  – respiratory distress (eg, pulmonary edema or large pleural effusions),
  – skin breakdown with an increased risk of cellulitis,
  – increases the risk of bacterial peritonitis.
Complications

- Thrombosis
- Renal insufficiency.
- Hypovolemia
Diagnosis

- Urinalysis: protein > 3+, +/- blood
- Quantitative protein analysis
  - Total daily excretion >50mg/kg/day
  - Urine protein : creatinine ratio > 0.2gm/mmol
- Serum albumin < 30g/dl
- Urea/electrolyte/creatinine
  - Calculate GFR height x coefficient/creatinine
- Lipid profile: hypercholesterolemia
Quantitative urine protein evaluation

- 24 hr urine collection is a myth in paediatrics!
- Nice to hear about it but not done world wide and difficult to do it for logistical reasons
- Spot urine protein: creatinine ratio valuable
  - >0.02 g/mmol-proteinuria
  - >0.2g/mm mol nephrotic range
- Comparable results to 24 hr urine collection

Other tests

- Blood count
- Hepatitis B, HIV, VDRL
- Complement studies
- Antinuclear antibodies
CASE

INVESTIGATIONS

• Pr/Cr ratio 1.5 (N <0.02g/mmol)

• Urea 5 Creat 40 umol/l
• Protein 38 Alb 9 Cholesterol 10
• FBC normal, ESR 114
• RVD negative
• Hep B negative and VDRL negative
• Mantoux non-reactive
• CXR- rt pleural effusion
Indications for biopsy

- Indications:
  1. Age <1 or >10 years
  2. Steroid resistance
  3. Steroid dependence or frequent relapse
  4. HTN, gross haematuria
  5. Deteriorating renal function
Nephrotic Syndrome Management

- Daily urine dipsticks
- Salt restriction
- No fluid restriction unless hypertensive or in renal failure
- Control severe oedema - IV albumin with diuretics
- Avoid diuretics on own – check perfusion.
- Prophylactic penicillin
- Aggressive treatment of infection
Treatment

• Prednisolone 2mg/kg/day for 6 weeks then 1.5 mg/kg alternate days for 6 weeks then taper off over 6 weeks (KDIGO)
• Most respond to treatment
• About 60% relapse
• Frequent relapsers are >2 relapse in 6 months
• Steroid resistance is proteinuria > 3 + at 4 weeks of treatment
Treatment

• Other modalities
  – Alkylating agents
    • Cyclophosphamide, chlorambucil
  – Calcineurin inhibitors
    • Cyclosporin, tacrolimus
  – MMF, azathioprine
  – ACE inhibitors
Renal Biopsy findings at KNH

- FSGS and steroid resistance: 84.8% of biopsies with steroid resistance had FSGS v/s 23.6% if indication something else ($p= 0.008$)
- Mean age 9.34yrs those without 8.34yrs
- Other factors like gender not different
## Treatment of steroid-resistant FSGS: Evidence-based recommendations

<table>
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<tr>
<th>Treatment</th>
<th>Recommendation</th>
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</thead>
<tbody>
<tr>
<td>Oral cyclophosphamide (12 weeks)</td>
<td>No benefit</td>
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<tr>
<td><strong>Cyclosporin (at least 6 months)</strong></td>
<td><strong>Beneficial</strong></td>
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<tr>
<td>IV methylpred and alkylating agents (6 months to 1 year)</td>
<td>Possible benefit</td>
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<tr>
<td>IV cyclophosphamide (monthly for 6 months)</td>
<td>Possible benefit</td>
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<tr>
<td>MMF</td>
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<td>Tacrolimus</td>
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<td>Plasmapharesis</td>
<td>Anecdotal reports</td>
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<td>High dose Enalapril</td>
<td>Useful in reducing proteinuria</td>
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Summary

• Nephrotic syndrome is a common paediatric renal condition
• It is important to make the diagnosis based on proteinuria, hypoalbuminemia, oedema and hypercholesterolemia
• Initiate treatment with steroids at the right dose
• Refer at the earliest as these patients complicate fast
Some things just don't hold water...