The Nephrotic Syndrome

Glomerular Disease associated with heavy albuminuria (> 3-3.5 g/day)

Hypoalbuminemia
Edema
Hyperlipidemia
Thrombotic tendency

Genesis of Hypoalbuminemia

Glomerular Disease
Proteinuria
Increased albumin catabolism
Hypoalbuminemia

Objectives – Nephrotic Syndrome

- Define the nephrotic syndrome.
- Review the mechanism of proteinuria.
- Discuss the mechanisms of the major manifestations of the NS – edema, hyperlipidemia, thrombotic tendency
- Discuss the clinical features and pathology of major clinical forms of the NS.
Pathogenesis of Nephrotic Edema

- Hypoalbuminemia:
  - Low oncotic pressure

- Na and Water retention:
  - High hydrostatic pressure

(Starling forces)

Pathogenesis of Edema

Therapy of Edema in NS

- Put pt on low Na+ diet
- Use oral loop diuretics
- Sart w low dose - double doses
  - add zaroxolyn
  - +/- high BID doses
- IV diuretics and colloid rarely needed
- Goal is 1-2 # edema loss/ day

Lipiduria and Oval Fat Bodies
### Treatment of Hyperlipidemia of the Nephrotic Syndrome

- Select high risk pt (high LDL, low HDL, unlikely to rapidly remit)
- Attempt to induce a remission of the proteinuria (ACEi/ARBs, specific immunosuppressives, etc.)
- Dietary Therapy
- Medical Therapy (statins +)

### Treatment Principles

- **Treatment of Primary Disease:** Often immune modulating medications
- **Symptomatic Treatment:** Diuretics, statins, diet, in some anticoagulation
- **Reduction of Proteinuria/Slowing Progression**
Reduction of Proteinuria and Slowing Progression

- Blood pressure reduction
- Inhibition of the renin-angiotensin-aldosterone axis

Meta Analysis: Lower Mean BP Results in Slower Rates of Decline in GFR in Diabetics and Non-Diabetics

\[ r = 0.69; \ p < 0.05 \]


ACE-I Is More Renoprotective than Conventional Therapy in Type 1 Diabetes

<table>
<thead>
<tr>
<th>% change in proteinuria</th>
<th>Placebo</th>
<th>Captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-20</td>
<td>-20</td>
</tr>
<tr>
<td>Captopril</td>
<td>-60</td>
<td>-60</td>
</tr>
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\( P < .001 \)


The Effect of ACE-I on Diabetic Nephropathy: The Collaborative Study Group

- Type 1 DM with Urine Alb>500mg/d

\( 48\% \) risk reduction


Case 1 – 8 year old child

- An 8 year old child presents with swelling of his eyes and ankles. He has 4+ proteinuria on urine dipstick
- Other labs:
  - BUN 8 mg/dl
  - Creatinine 0.5 mg/dl
  - Albumin 2.2 g/dl, serum cholesterol 400mg/dL
  - 24 hour urine protein 6.0 g/day (normal <150mg)
- Serologic tests are negative or normal
Evidence for Immunologic Derangements in Nil Disease

- Viral infections may precede onset or recrudescences.
- May follow recent immunizations.
- Altered in vitro response to mitogens.
- Circulating lymphocytotoxins.
- Altered lymphocyte subpopulations.
- ↑ HLA B-12
- Association with Hodgkin’s Disease and other lymphoproliferative disease

Synonyms

- Minimal Change Disease
- Nil Disease
- Lipoid Nephrosis
- Childhood Nephrosis

Puromycin Aminonucleoside Nephrosis
Minimal Change Disease

- 5-10% Adults with NS, >85% children
- Usually sudden onset, hvy proteinuria, and edema
- HBP 30%, Microhem 30 %, +/- Low GFR (volume depletion)
- Pathology: LM-Ni, IF-Neg, EM-FFP
- Course: Respond to Strds, Relapse, No RF

Case 1: Treatment and Course

- Prednisone 1mg/kg was started
- Furosemide was prescribed for edema
- 3 weeks later the patient was edema-free.
- Urine dipstick tests for protein were negative.
- Prednisone was tapered and stopped by the third month

Case 2

- A 19 year old female college student gains 12 pounds and has lower extremity edema. Her physician finds 4+ albuminuria.
- Labs:
  - Creatinine 1.0 mg/dl
  - Albumin is 2.0 g/dl
  - Cholesterol 425 mg/dl
  - 18g proteinuria/day
  - Serologic tests are negative
- Corticosteroid treatment is without improvement
MCD and FSGS

- Separate or related entities?

<table>
<thead>
<tr>
<th>Circulating Factors in MCD and FSGS:</th>
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<tbody>
<tr>
<td>Ref.</td>
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<tr>
<td>------</td>
</tr>
<tr>
<td>Bakker 1996</td>
</tr>
<tr>
<td>Koyama 1991</td>
</tr>
<tr>
<td>Savin 1996</td>
</tr>
<tr>
<td>Dantal 1994</td>
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</tbody>
</table>
Secondary FSGS due to Adaptive Responses
- Reflux nephropathy
- Renal agenesis (solitary functioning kidney)
- Any Chronic Renal Disease
- Obesity

Obesity-Glomerular “Stress”
Focal Segmental Glomerulosclerosis

- Increased frequency > 20% NS – Blacks!
- In adults onset 2/3 NS, 1/3 proteinuria
- HBP > 30%, Microhematuria >30%, renal dysfunction 50%
- Predictors of ESRD: hvy prot., Blks, high creatinine, on BX – int fibrosis & Collapse
- Strds >50% respsond, cytoxan, cyA, MMF
- Recurs 1/3 Txps-

Case 3

- A 67 year old Caucasian Male develops ankle edema and weight gain.
- Labs:
  - 12 g proteinuria/day
  - GFR normal (creatinine 1.1 mg/dl)
  - Albumin of 1.4 g/dl
  - Cholesterol 635 mg/dl
Conditions Associated with Membranous Glomerulopathy

- **Infections**
  - Hepatitis B, Hepatitis C, secondary and congenital syphilis, malaria, schistosomiasis
- **Drugs**
  - Gold, penicillamine, captopril
- **Collagen vascular disease**
  - SLE, Hashimoto’s thyroiditis, Rheumatoid Arthritis
- **Neoplasia**
  - Carcinoma (lung, breast, colon, stomach)

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**Membranous Nephropathy**

- The most common etiology of idiopathic nephrotic syndrome in white adults
- Course variable
- Renal survival at 10 y: 65%-85%
- Renal survival at 15 y: 60%
- Spontaneous remission rate: 20%-30%
Treatment of Membranous Nephropathy

- Conservative Therapy
- Corticosteroids
- Alternating Steroids –Cytotoxics
- Cyclosporine
- Mycophenolate
- Anti C5 Ab, Rituximab

Case 3: Post Biopsy Course

- All serologic tests are normal
- Normal Colonoscopy and CT abdomen/chest
- 3 days after admission, he develops a dull back ache and then becomes acutely short of breath.
- Chest X-ray is normal
- ABG: pH=7.45 pCO2=30, pO2 =60 on room air
- CT angiogram is requested

CT angiogram: Abdomen

CT angiogram: Chest

Thrombotic Abnormalities in the Nephrotic Syndrome

- Increased coagulation tendency ( plat. hyperaggregability, high fibrinogen and fibrinogen-fibrin transfer, decreased fibrinolysis, low anti-thrombin III )
- DVT, RVT, pulmonary emboli
- Membranous NS greatest risk (up to 35% )
- Most RVT asymptomatic, but flank pain, microhematuria, low GFR
Case 4

- A 38 year AA female has had Type 1 diabetes since the age of 19.
- She has severe retinopathy and multiple admissions for labile blood sugars.
- Her internist refers her for proteinuria which has gone up from 200mg/day to 3.2 grams. Her serum creatinine is 1.5mg/dL.
- She has experienced a 22 pound weight gain and pitting edema to her thighs.
- She is on twice/daily insulin and Diltiazem.

Case 4: Physical Exam

Case 4: Ophthalmologic Exam
Types of Diabetes Mellitus

- **Type I - Insulin Dependent** (hypoinsulinemic, ketotic, juvenile onset)
- **Type II - Non-Insulin Dependent** (Normoinsulinemic, non-ketotic, maturity onset)

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**Basement Membrane Thickening in Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Vascular BM</th>
<th>Other BM</th>
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<tbody>
<tr>
<td>Glomerular Capillaries</td>
<td>Renal Tubules</td>
</tr>
<tr>
<td>Muscle Capillaries</td>
<td>Mammary Ducts</td>
</tr>
<tr>
<td>Retinal Capillaries</td>
<td>Schwann Cells</td>
</tr>
<tr>
<td>Arterioles</td>
<td></td>
</tr>
</tbody>
</table>

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Diabetic Nephropathy

- Nonenzymatic Glycosylation Glom BM
  - Accumulation circulating plasma proteins
  - Static acid content
  - Cationic charge
  - Disulfide bonding GBM collagen
  - Defective mesangial clearing
  - Mesangial sclerosis
  - Proteinuria
  - GBM degradation
  - GBM Synthesis
  - GBM thickening
Stages of Diabetic Renal Disease
Type 1 Diabetes

- Stage 1: Hyperfiltration
- Stage 2: Clinically silent
- Stage 3: Incipient Nephropathy
  - AER: 20-200ug/min
- Stage 4: Overt Nephropathy
- Stage 5: ESRD

Progression of Diabetic Nephropathy

Current Strategies to Limit Renal Injury in Diabetic Nephropathy

- Blood pressure reduction
- Inhibition of the renin-angiotensin-aldosterone axis
- Blood sugar control
- Metabolic manipulation

Blood Pressure Targets

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>BP Goal</th>
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<tbody>
<tr>
<td>Hypertension (no diabetes or renal disease)</td>
<td>&lt;140/90 mmHg (JNC 7)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>&lt;130/80 mmHg (ADA, JNC 7)</td>
</tr>
<tr>
<td>Renal Disease with proteinuria &gt;1 gram/day or diabetic kidney disease</td>
<td>&lt;130/80 mmHg &lt;125/75 mmHg (NKF)</td>
</tr>
</tbody>
</table>

Case 4: Follow up

- Symptomatic
  - Furosemide 80mg + Metolazone 5mg
  - Pravastatin 40mg
- Reduction of Proteinuria
  - Ramipril 10mg + Candesartan 16mg/day
- Edema improved and proteinuria decreased to 200mg/day
- Her GFR however gradually deteriorated over 6 years and she is on hemodialysis awaiting a kidney transplant.
Case 5

- A 66 y o housewife with severe rheumatoid arthritis for 22 years develops edema. She is currently taking no medications.
- Labs:
  - 9 g proteinuria/day
  - Serum creatinine 1.2mg/day
  - Serologic tests are negative
  - Creatinine clearance of 100 cc/min

Rheumatoid Hands
Amyloid

- LM: A homogenous, hyaline eosinophilic proteinaceous substance.
  - Special Stains:
    - Congo Red
    - Methyl Violet
    - Thioflavin T
  - EM:
    - Fibrillar Constituent
      - Random arrays of non-branching fibrils, 80-100Å in width, beading with 55Å periodicity
    - Non-Fibrillar Constituents
      - Pentameric discs (AP protein)
    - X-ray Diffraction: beta pleated sheet conformation

Amyloidosis

<table>
<thead>
<tr>
<th>Cause</th>
<th>Type</th>
<th>Precursor Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dysproteinemias Primary</td>
<td>Primary</td>
<td>Light chains</td>
</tr>
<tr>
<td>2. Longstanding inflammatory</td>
<td>Secondary</td>
<td>SAA-protein (acute phase</td>
</tr>
<tr>
<td>or infectious states</td>
<td>“AA”</td>
<td>reactant)</td>
</tr>
</tbody>
</table>

Chronic Diseases Associated with “AA” Amyloidosis

- Tuberculosis
- Leprosy
- Chronic Osteomyelitis
- Paraplegia
- Chronic bronchiectasis
- Cystic Fibrosis
- Chronic Heroin Addiction
- Rheumatoid Arthritis
- Psoriasis
- Familial Mediterranean Fever
Case 5: follow up

- Symptomatic treatment
  - HCTZ 25mg qd
- Reduction of proteinuria
  - Lisinopril 10mg/day
- Rheumatoid Arthritis
  - Anti TNF therapy

Conclusions

- Glomerular disease due to the Nephrotic Syndrome (nephrosis) is a common cause of renal disease.
- A renal biopsy and good nephropathologist are essential in diagnosis
- Treatment includes BP control, use of ACE-inhibitors in addition to specific and symptomatic therapy.

The End
(Et Cetera!)