The Nephrotic Syndrome

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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.
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
Pathogenesis of Nephrotic Edema

- Hypoalbuminemia:
  - Low oncotic pressure
- Na and Water retention:
  - High hydrostatic pressure

(Starling forces)
Pathogenesis of Edema

- Glomerular Disease
  - Proteinuria
  - Increased Fractional Albumin Catabolism
  - Hypoalbuminemia
    - Plasma Oncotic Pressure
      - Capillary Filtration
        - Plasma Volume
          - Secondary Renal Sodium Retention
    - EDEMA
Pathogenesis of Edema

Glomerular Disease

Proteinuria → Hypoalbuminemia

Primary Renal Sodium Retention

Plasma Volume

Capillary Filtration

EDEMA
Pathogenesis of Edema

A. ADR

B. Saline

Graph showing Na excretion, µEq/min over time (minutes) with ANP infusion.
Therapy of Edema in NS

- Put pt on low Na+ diet
- Use oral loop diuretics
- Start 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
Total Cholesterol Levels in 100 Consecutive Nephrotic Synd. Pts

- >200 mg/dl: 100 NS, 87 Memb NS, 53 FSGS
- >300 mg/dl: 100 NS, 53 Memb NS, 25 FSGS
- >400 mg/dl: 100 NS, 25 Memb NS, 25 FSGS
LDL Cholesterol Levels in 100 Consecutive Nephrotic Synd. Pts

- >130 mg/dl: 77
- >160 mg/dl: 65

Legend:
- 100 NS
- Memb NS
- FSGS
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 +)
LOVASTATIN EFFECTS ON LIPIDS IN THE NEPHROTIC SYNDROME

Lovastatin Dose

Baseline Placebo 10 mg BID 20 mg BID 40 mg BID

mg/dL  mM/L
400  10.4
Total Cholesterol
350  9.1
300  8.1
250  7.8
200  7.5
150  7.2
100  6.9
50   6.6
0    6.3

mg/dL  mM/L
350  3.96
325  3.67
300  3.39
275  3.11
250  2.82
225  2.64
200  2.46
175  2.26
150  2.08
125  2.00
100  1.82
75   1.64
50   1.46
25   1.28
0    1.10

Time (Weeks)

Plasma Cholesterol

Plasma Triglycerides

LDL-Cholesterol

Triglycerides

HDL-Cholesterol

mg/dL  mM/L
50   1.3
100  2.6
150  3.9

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

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

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

Case 1 – 8 year old child
Case 1

- 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 400 mg/dL
  - 24 hour urine protein 6.0 g/day (normal <150 mg)
- Serologic tests are negative or normal.
Synonyms

- Minimal Change Disease
- Nil Disease
- Lipoid Nephrosis
- Childhood Nephrosis
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.
- Association with Hodgkin’s Disease and other lymphoproliferative disease
Animal Model
Puromycin Aminonucleoside Nephrosis
Minimal Change Disease

- 5-10% Adults with NS, >85% children
- Usually sudden onset, heavy proteinuria, and edema
- HBP 30%, Microhem 30 %, +/- Low GFR (volume depletion)
- Pathology: LM-Normal, IF-Neg, EM-FPF
- Course: Respond to Steroids, 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?
## Circulating Factors in MCD and FSGS:

<table>
<thead>
<tr>
<th>Ref</th>
<th>Source</th>
<th>Biologic Activity</th>
<th>Biochemical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakker</td>
<td>Serum or mononuclear cells of MCD</td>
<td>Increases vasc. permeability</td>
<td>~ 120 Kd Kallikrein-like</td>
</tr>
<tr>
<td>1986</td>
<td></td>
<td>Binds anionic sites</td>
<td></td>
</tr>
<tr>
<td>Koyama</td>
<td>T cell hybridoma from MCD</td>
<td>Causes proteinuria and foot process fusion in rats</td>
<td>60-160 Kd Not an Ig</td>
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<tr>
<td>1991</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Savin</td>
<td>Serum or plasma of FSGS (initial, collapsing, recurrent) and steroid-resistant MCD</td>
<td>Increases glom permeability in vitro</td>
<td>50 Kd Binds protein A Not Ig</td>
</tr>
<tr>
<td>1996</td>
<td></td>
<td></td>
<td>Not Cationic</td>
</tr>
<tr>
<td>Dantal</td>
<td>Plasma of recurrent FSGS in txp</td>
<td>Causes proteinuria and foot process fusion in rats</td>
<td>&lt; 100,000 Kd Binds protein A</td>
</tr>
<tr>
<td>1994</td>
<td></td>
<td></td>
<td>Not Ig</td>
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</table>
Secondary FSGS due to Adaptive Responses

- Reflux nephropathy
- Renal agenesis (solitary functioning kidney)
- Any Chronic Renal Disease
- Obesity
What if We Are Really Evolving?
Obesity-Glomerular “Stress”

...AND YOU THINK YOU HAVE STRESS...
Loss of Functioning Nephrons

 Increased Glomerular Volume

 Capillary Radius

 Tension of GCW

 Microaneurysms

 Segmental Capillary Collapse Mesangial Sclerosis
Pathogenetic Factors (Known and Hypothetical) in FSGS

- Hemodynamic
  - Glomerular Hyperfiltration
  - Glomerular Hypertrophy

- Genetic
  - Glomerular Hyperfiltration
  - Glomerular Hypertrophy

- Immunologic
  - "Permeability" Factors
  - Adriamycin
  - Puromycin
  - HIV

- Toxic
  - Adriamycin
  - Puromycin

- Viral
  - HIV

- Visceral Cell Injury
  - Mesangial Injury
    - Cytokines/Mitogens
      - Glomerulosclerosis
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% respond, 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)
GENERATION OF HEYMANN NEPHRITIS

FX1A (fractioned material from renal cortex)

RAT

SERUM

RAT

ACTIVE HEYMANN NEPHRITIS

PASSIVE HEYMANN NEPHRITIS
CONSEQUENCES OF IMMUNE DEPOSIT FORMATION

BINDING OF COMPLEMENT → FORMATION OF THE C5b-9 COMPLEX → ACTIVATION OF GVEC
Scavenging of C5b-9
Increased expression of cytochrome b_{558}

FORMATION OF REACTIVE OXIGEN SPECIES (ROS) → DEPOSITION OF ROS IN GBM

PROTEINURIA
Discovery of the Target Antigen in Human Membranous Glomerulopathy!!!!!
(Salant et al. NEJM 2009)

• PHOSPHOLIPASE A2 RECEPTOR (PLA2R)

Antibody to PLA2R has been eluted from glomerular deposits of human MGN
Antibody to PLA2R is detected in serum of 70% of patients with primary MGN
Membranous Nephropathy

- The most common etiology of 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

BP : 160/102
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)
MUTATION: SURVIVE FAMINE
THEN: ADEQUATE FOOD
TODAY: SUPERABUNDANT FOOD

EVOLUTION: Not Always - Obviously - Favorable
Basement Membrane Thickening in Diabetes Mellitus

Vascular BM
- Glomerular Capillaries
- Muscle Capillaries
- Retinal Capillaries
- Arterioles

Other BM
- Renal Tubules
- Mammary Ducts
- Schwann Cells
Diabetic Nephropathy

Nonenzymatic Glycosylation Glom BM

Accumulation circulating plasma proteins

↓ Sialic acid content

↑ Cationic charge

↑ Disulfide bonding GBM collagen

↓ GBM degradation

↑ GBM Synthesis

↑ GBM thickening

Defective mesangial clearing

↓ Mesangial sclerosis

Proteinuria
Stages of Diabetic Renal Disease
Type 1 Diabetes

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

Mesangial Expansion

Microalbuminuria

GBM Thickening

Proteinuria

Glomerulosclerosis
Progression of Diabetic Nephropathy

- Microalbuminuria: Early stage
- Proteinuria: Late stage
- ESRD: End stage
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 (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>
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<tbody>
<tr>
<td>1. Dysproteinemias</td>
<td>Primary “AL”</td>
<td>Light chains</td>
</tr>
<tr>
<td>2. Longstanding inflammatory or infectious states</td>
<td>Secondary “AA”</td>
<td>SAA-protein (acute phase 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!)