Proteinuria
Nephrotic syndrome

Pathophysiology & management

Miriam Davidovits, MD
Institute of Nephrology
Schneider Children's Medical Center of Israel

Abnormal excretion of protein into the urine is one of the most important pathophysiological disturbances accompanying renal disease.

Daily Glomerular Filtration
180 Liters

Protein Content
12 Kilograms
Protein composition of final urine

Glomerular filtration of proteins present in plasma

+ Tubular reabsorption of filtered protein

+ Addition or secretion of protein into urine throughout the genitourinary tract

Podocyte proteins

*Lancet* 2003
Pathophysiology of Proteinuria

- Decreased size selectivity
- Decreased charge selectivity

Albumin concentration of normal glomerular filtrate:

<table>
<thead>
<tr>
<th>Recent observations:</th>
<th>0.1 - 1mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sieving coefficient</td>
<td>0.1mg/dl</td>
</tr>
<tr>
<td>Sieving coefficient for:</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>&gt; 0.5</td>
</tr>
<tr>
<td>Growth hormone</td>
<td></td>
</tr>
<tr>
<td>β₂-Microglobulin</td>
<td></td>
</tr>
<tr>
<td>Light chains</td>
<td></td>
</tr>
</tbody>
</table>

Larger plasma proteins (albumin, IgG) are all reabsorbed by a common mechanism. Increasing the filtered load of one protein would consequently decrease the reabsorption and increase the urinary excretion of all the competing proteins. A separate mechanism exists for the reabsorption of low-molecular-weight proteins.
TUBULAR PROTEINURIA

- The urinary excretion of small proteins (MW 5,000 - 50,000) is increased many fold
- Failure of tubular protein reabsorption results in only mild or moderate proteinuria! (usually <1gr/day)
- The measured excretion of most LMW proteins is increased and any of several LMV proteins can be used for diagnostic purposes
- The reabsorption of albumin is only minimally affected

DIAGNOSIS OF TUBULAR DYSFUNCTION:

Increased excretion of small proteins is a sensitive indication of proximal tubular injury or dysfunction.

ALL LMW protein reabsorption is affected

Normal: Urine β2-Microglobulin <0.4mg/l
>3mos of age
Newborn: >4mg/l
Lysozyme: 1mg/dl

RENAL TUBULAR PROTEIN HANDLING IN FIRST MONTH OF LIFE:

Urine protein excretion x 2
Urinary LMW Proteins >> albumin

Conclusion:
The higher protein excretion results from less complete tubular reabsorption

COMPARISON OF METHODS OF MEASURING URINARY PROTEIN CONCENTRATION

<table>
<thead>
<tr>
<th>Protein concentration mg/dL</th>
<th>Dipstick</th>
<th>Sulfosalicylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>No turbidity</td>
</tr>
<tr>
<td>1-10</td>
<td>Trace</td>
<td>Slight turbidity</td>
</tr>
<tr>
<td>15-30</td>
<td>1+</td>
<td>Turbidity through which print can be read</td>
</tr>
<tr>
<td>40-100</td>
<td>2+</td>
<td>White cloud without precipitate through which heavy black lines on white background can be seen</td>
</tr>
<tr>
<td>150-350</td>
<td>3+</td>
<td>White cloud with fine precipitate through which heavy black lines cannot be seen</td>
</tr>
<tr>
<td>500</td>
<td>4+</td>
<td>Flocculent precipitate</td>
</tr>
</tbody>
</table>
DEFINITION OF PROTEINURIA

- Adults >150mg/24hr
- Children > 4mg/m²/hr
  - protein(mg/dl) : creatinine(mg/dl) > 0.2
- Nephrotic range proteinuria > 40mg/m²/hr
  - protein(mg/dl) : creatinine(mg/dl) > 2

Normal Urinary Protein Composition

- Albumin 15 -20%
- Tamm-Horsfall Glycoprotein 50-60%
- Immunoglobulins 15%
- Other Plasma Proteins 5%

DEFINITION OF ALBUMINURIA

- Adults <30mg/24hr
- Adults and Children
  - albumin(mg) : creatinine(mg) < 0.03
  - albumin(mcg) : creatinine(mg) < 30

Microalbuminuria

- Elevated urine albumin excretion below the level of detection by routine protein dipstick test
  - 30 -300 mg/24 hours
- Persistent rates of urinary albumin excretion above
  - 20mcg/minute
- are predictive of subsequent diabetic nephropathy and other chronic renal diseases
**ORTHOSTATIC PROTEINURIA**

- Abnormally high protein excretion in upright position only
- Protein excretion must not exceed the normal limits when the subject is recumbent
- Total protein excretion rarely exceeds 1gr/day

**Pathophysiologic Mechanism:**
- Altered renal hemodynamic response to orthostasis

---

**THE NEPHROTIC SYNDROME**

**DEFINITION**

- PROTEINURIA
- HYPOALBUMINEMIA
- EDEMA

**COMPLICATIONS OF NEPHROTIC SYNDROME**

**HYPERLIPIDEMIA**

Albumin < 3 g/dl → Cholesterol increase
Albumin < 2 g/dl → Triglycerides increase

**Mechanisms**

1. **Plasma oncotic pressure decrease**
   Increased hepatic synthesis of Lipoproteins (LDL, VLDL)

2. **Lipoprotein Lipase Activity inhibition**
   \[ Alb \downarrow \text{FFA} \] \quad HDL Lipoproteinuria

3. **L-CAT loss in urine**
COMPLICATIONS OF NEPHROTIC SYNDROME

HYPERCOAGULABILITY

- Urinary loss of antithrombin III, protein S, protein C
- Increased production of plasma clotting factors
- Increased thrombocyte aggregation
- Intravascular volume depletion and hyperviscosity

SUSPECTIBILITY TO INFECTIONS

A. Urinary loss or decreased production of IgG
B. Urinary loss of alternative complement pathway factor B
C. Impaired granulocyte chemotaxis
D. Presence of gross edema and ascites
E. Immunosuppressive therapy

IMPAIRED GROWTH

A. Protein - calorie malnutrition
   Poor appetite
   Malabsorption due to edema of the GI tract

B. Corticosteroid therapy
   GH - Normal
   Peripheral resistance to IGF-1 action
   Direct target cell damage

ETIOLOGY OF CHILDHOOD NEPHROTIC SYNDROME

PRIMARY RENAL CAUSES

- Minimal change nephropathy
- Focal segmental glomerulosclerosis
- Mesangial proliferation

Immune complex glomerulonephritis
- Membranoproliferative glomerulonephritis
- Membranous nephropathy
- Acute postinfectious glomerulonephritis
- Congenital nephrotic syndrome
ETIOLOGY OF CHILDHOOD NEPHROTIC SYNDROME

SYSTEMIC CAUSES

Infectious - Syphilis, malaria
Toxins - Penicillamine, pamidronate, NSAIDS
Allergies - Bee sting, food allergy, asthma
Cardiovascular - Renal vein thrombosis, congestive heart failure
Malignancies - Hodgkin's disease, Leukemia
Others - SLE, Henoch-Shonlein purpura

MINIMAL CHANGE NEPHROTIC SYNDROME

The largest group (75-84%) of childhood nephrotic syndrome

Definition:
- Normal light microscopy
- Immunofluorescence - negative
- EM - fusion of epithelial foot processes

COMPLICATIONS OF NEPHROTIC SYNDROME

HYPERCOAGULABILITY

- Urinary loss of antithrombin III, protein S, protein C
- Increased production of plasma clotting factors
- Increased thrombocyte aggregation
- Intravascular volume depletion and hyperviscosity

SUSCEPTIBILITY TO INFECTIONS

A. Urinary loss or decreased production of IgG
B. Urinary loss of alternative complement pathway factor B
C. Impaired granulocyte chemotaxis
D. Presence of gross edema and ascites
E. Immunosuppressive therapy
COMPLICATIONS OF NEPHROTIC SYNDROME

IMPAIRED GROWTH

A. Protein - calorie malnutrition
   Poor appetite
   Malabsorption due to edema of the GI tract

B. Corticosteroid therapy
   GH - Normal
   Peripheral resistance to IGF-1 action
   Direct target cell damage

ETIOLOGY OF CHILDHOOD NEPHROTIC SYNDROME

PRIMARY RENAL CAUSES

- Minimal change nephropathy
- Focal segmental glomerulosclerosis
- Mesangial proliferation

Immune complex glomerulonephritis
- Membranoproliferative glomerulonephritis
- Membranous nephropathy
- Acute postinfectious glomerulonephritis
- Congenital nephrotic syndrome

ETIOLOGY OF CHILDHOOD NEPHROTIC SYNDROME

SYSTEMIC CAUSES

Infectious - Syphilis, malaria
Toxins - Penicillamine, pamidronate, NSAIDS
Allergies - Bee sting, food allergy, asthma
Cardiovascular - Renal vein thrombosis, congestive heart failure
Malignancies - Hodgkin's disease, Leukemia,

Others - SLE, Henoch-Shonlein purpura

MINIMAL CHANGE NEPHROTIC SYNDROME

The largest group (75-84%) of childhood nephrotic syndrome

Definition:
- Normal light microscopy
- Immunofluorescence - negative
- EM - fusion of epithelial foot processes
MINIMAL CHANGE NEPHROTIC SYNDROME

DOMINANT CLINICAL FEATURES

- Age: 1-6 years
- Absence of hematuria
- Normal renal function
- Normal blood pressure
- Normal complement level
- Response to initial treatment with prednisone

INDICATIONS FOR KIDNEY BIOPSY IN CHILDHOOD NEPHROTIC SYNDROME

- Evidence of systemic disease
- Nephritic features
- Steroid resistance
INITIAL PREDNISONE TREATMENT

I. 60mg/m\(^2\)/day for 6 weeks

II. 60mg/m\(^2\)/48hr for 4 weeks

III. Tapering off by 5mg/m\(^2\)48 hr every 2 weeks

Metaanalysis of 12 randomized controlled trials (868 children):

Inverse linear correlation between duration of prednisone therapy and risk of relapse

Arch Dis Child, 2003

MINIMAL CHANGE DISEASE

Responders

93%

Initial Nonresponders

7%

Non-relapsers

31%

Infrequent relapsers

31%

Frequent relapsers

Steroid Dependent

31%

50%
**MCNS - TREATMENT OF RELAPSE**

I. 60mg/m²/day until response

II. 60mg/m²/48h for 2 weeks

III. Tapering off by 5mg/m²/48h every 2 weeks

---

**Alternative Immunosuppressive Therapy**

*Indications: Frequently Relapsing/Steroid Dependent MCNS with Steroid Toxicity*

- 1. Mycophenolate mofetil (Cell-Cept)
  - 400-600mg/m²/dose BID
- 2. Cyclosporine 3-5 mg/kg/d  BID
  - Tacrolimus 0.1mg/kg/d  BID
- 3. Cyclophosphamide 2-3 mg/kg/d for 8 weeks with intermittent prednisone
- 4. Levamisole 2.5-3 mg x 3/week 6-12m
- 5. Rituximab (Mabtera) IV 375mg/m² 1-4 doses
TREATMENT OF MCNS

**Supportive Care**
- Salt restriction
- Protein intake: 75-100% RDA
- Diuretics
- Prophylactic antibiotic therapy
- **Vaccinations** (conjugated pneumococcal vaccine, Varicella)

**Immunosuppressive Drugs**

MCNS

- Long-term prognosis: excellent
- **Most important predictive factor:** Response to initial Prednisone therapy
- **Mortality:** 2-5%

Steroid-resistant idiopathic nephrotic syndrome

Focal Segmental Glomerulosclerosis

Diffuse Mesangial Proliferation

Minimal Change Disease

Focal Segmental Glomerulosclerosis

- Primary Nephrotic Syndrome - 10%
- Steroid Resistant NS - 40%
- End – Stage Renal Failure - 12%
PRIMARY NEPHROTIC SYNDROME

<table>
<thead>
<tr>
<th></th>
<th>FSGS</th>
<th>MCNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of hematuria</td>
<td>48%</td>
<td>22.7%</td>
</tr>
<tr>
<td>Incidence of hypertension</td>
<td>33.4%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Response to Prednisone</td>
<td>25.0%</td>
<td>93.7%</td>
</tr>
</tbody>
</table>

TREATMENT OF FSGS/SRNS

1. Prednisone (25% response)
2. Cyclophosphamide (14-20% response)
3. Methylprednisolone Pulses (Mendoza protocol-66% response)
4. Cyclosporine (19-43% response)
5. Tacrolimus/Cyclosporine + Cell-Cept
6. Rituximab

TRANSPLANTATION IN FSGS

Recurrence range 30-60%
-2nd graft 85-100%

Pathogenesis:
GBM damage due to a circulating soluble permeability factor

Treatment:
Immediate plasmapheresis + cyclophosphamide/cyclosporine + Rituximab
CLASSIFICATION OF CONGENITAL AND INFANTILE NEPHROTIC SYNDROME

- **Idiopathic** CNS of Finnish type
  - Diffuse Mesangial Sclerosis
  - Other Glomerular diseases (MCNS, FSGS)

- **Secondary** Congenital Syphilis
  - Toxoplasmosis, Rubella, CMV
  - Hepatitis, HIV, Malaria
  - SLE

- **Syndromic** Denys-Drash
  - Nail-patella
  - CNS with brain malformation

CNS of Finnish Type - Clinical features

- Intrauterine proteinuria (alpha-fetoprotein-AFP)
- Prematurity (80%)
- Low-birth-weight
- Placentomegaly
- Severe proteinuria at birth
- Serum albumin < 1gr/dl
- Normal GFR during first 6 months of life

CNS of Finnish Type - Management

- Intensive nutritional support

- Nephrectomy - bilateral + dialysis
  - or: unilateral + ACEi + NSAIDS

- Transplantation: recurrence in graft
  - (immunological response to nephrin)

CNS of Finnish Type - Prenatal diagnosis

- High maternal serum AFP

- Elevated amniotic fluid AFP
  - (250000-500000mcg/liter)

  **Carriers**: AFP up to 100000mcg/liter with later decrease