Proteinuria & Nephrotic Syndrome

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Objectives

- What is normal & abnormal urinary protein excretion?
- What is pathological proteinuria?
- Nephrotic syndrome and its causes in children.
- Management of nephrotic syndrome.
- What is microalbuminuria?

Normal urinary protein

Less than 4 mg/m²/hr (100 mg/m² per day) or total of 150 mg/day.

In neonates the protein excretion can be as high as 300 mg/m² per day.

Abnormal urinary protein

More than 4 mg/m²/hr (100 mg/m² per day).

Nephrotic: > 40 mg/m²/hr (1000 mg/m² per day).

Non-nephrotic: abnormal proteinuria that is less than nephrotic range.

Urinary protein composition

Types of proteinuria
Gold standard is to measure the protein in a timed urine collection. That is impractical most of the times.

Dipstick (screening method):
- Trace: between 15 & 30 mg/dl
- 1+: between 30 & 100 mg/dl
- 2+: between 100 & 300 mg/dl
- 3+: between 300 & 1000 mg/dl
- 4+: > 1000 mg/dl

Dipstick is specific for albumin. Dipstick readings are affected by urinary concentration.

Quantification of proteinuria

Urine protein to creatinine ratio:
- Normal < 0.2, Nephrotic > 2.0
- mg/dl : mg/dl < 0.2 is normal

Dipstick is specific for albumin.

Non-pathological proteinuria

Majority of the proteinuria cases in children are non-pathological where proteinuria is either transient or orthostatic.

Transient proteinuria can be present in a variety of conditions such as febrile illness, after exercise, during stress, episodes of seizures, and dehydration.

Orthostatic proteinuria

- Benign condition present in up to 5% of adolescents.
- Proteinuria only during ambulation.
- Most common cause of isolated proteinuria picked up during routine physical examination.
- Diagnosis is made by checking split urine collection or the first morning urine specimen for protein excretion.
- Proteinuria is usually < 1 gram per day.
- Orthostatic proteinuria resolves in most of the cases (50% by 10 years, 80% by 20 years).

Pathological proteinuria

Abnormal amount of urinary protein that is persistent and also present in the 1st morning void is pathological proteinuria.

Presentation:
- Symptoms /signs of renal disease: edema, hematuria, hypertension, abnormal renal function
- Symptoms /signs of systemic disease: fever, rash, joint pains.
- Asymptomatic.

Nephrotic Syndrome

- Proteinuria (cardinal feature)
- Hypoalbuminemia
- Edema
- Hyperlipidemia
Causes of Nephrotic Syndrome

Primary idiopathic (90%):
- 80% minimal change disease (MCD)
- 15% focal segmental glomerulosclerosis (FSGS)
- 5% diffuse mesangial hypercellularity (DMH)

Secondary:
- Lupus nephritis, IgA nephropathy, Henoch Schonlein purpura, malignancies, drugs, infections (malaria, hepatitis B, schistosomiasis), membranous nephropathy, MPGN.

Congenital nephrotic syndrome.

Nephrotic Syndrome (Epidemiology)

- Incidence: 1 in 6,000
- 80% patients younger than 6 years
- Twice as common in boys

MCD vs. FSGS

Electron Microscopic Findings

- Effacement of the foot processes

Laboratory findings

- Nephrotic proteinuria
- Hypoalbuminemia
- Hyperlipidemia
- Hyponatremia
- Mild azotemia
- Thrombocytosis
- Normal serum complements

Management (non-specific)

- Low sodium diet
- Diuretics
- Penicillin prophylaxis
- Aspirin
- Albumin infusion
- Vaccinations
Management (specific)

Steroids (prednisone / prednisolone):
- 2 mg/kg (60 mg/m²; maximum dose 80 mg) per day in two divided doses for 4 weeks
- 2 mg/kg every other day AM dose for 4 weeks
- Slow taper by decreasing the dose by 25% every 2 weeks
- Prolonged treatment of initial episode has been shown to decrease the incidence of relapses

Usual outcome

Response: in most cases proteinuria resolves by 2 weeks and in almost all by 4 weeks.
- > 90% with MCNS respond to steroids
- < 50% with FSGS respond to steroids

Typically over two-thirds of patients will have a relapsing course

Outcomes

Response, no relapse
Response with infrequent relapses
Response with frequent relapses
Steroid dependent
Late non-responder
Early non-responder (steroid resistant)

Management of relapse

Steroids (prednisone / prednisolone):
- 2 mg/kg (60 mg/m²; maximum dose 80 mg) per day in two divided doses until urine negative for protein for 3 consecutive days.
- 2 mg/kg every other day AM dose for 4 weeks.
- No tapering is required.

Management of steroid resistance

Multiple regimens: combination of immunosuppressive medications:
- High dose solumedrol with alkylating agents (Mendoza protocol).
- Cyclophosphamide.
- Chlorambucil.
- Cyclosporine.
- Tacrolimus.
- Mycophenolate mofetil.
- Levamesol (immunomodulator)

Complications

The two most common complications of nephrotic syndrome are infection and thrombosis.

Infections:
Most common infection is peritonitis and most common organism S. pneumoniae. Reasons for increased risk of infections: low levels of IgG, low factor B, impaired lymphocyte function, and immunosuppressive medications.

Thrombosis:
Reasons for increased risk of thromboembolism include low antithrombin III, high fibrinogen, increase in platelet aggregability, and hyperviscosity.
**Steroid side effects**
- Short stature
- Osteoporosis
- Obesity
- Cushingoid features
- Cataracts
- Avascular necrosis of head of femur
- Diabetes
- Pseudotumor cerebri

**Long-term prognosis**
Determined by response to steroid therapy, irrespective of underlying histopathology

Practical classification:
Steroid sensitive or steroid resistant nephrotic syndrome

**Indications for Kidney Biopsy**
- Steroid resistance
- Low serum complement levels
- Age < 1 or > 10 years
- Atypical features: hematuria, hypertension, persistent renal insufficiency
- Features of systemic illness

**Non-nephrotic range proteinuria**
Evaluation of persistent non-nephrotic range proteinuria depends on:
- Degree of proteinuria
- Patient's age
- Associated renal symptoms (hematuria, azotemia, hypertension etc.)
- Associated systemic features (rash, joint pains etc.)

**Microalbuminuria**
- Microalbuminuria is micro quantities of albumin that cannot be detected by dipstick and routine lab test.
- Normal rate of albumin excretion is < 30 mg/day (15 ug/min) Urine albumin to creatinine (mg/mg) ratio < 0.03
- Persistent values between 30 & 300 mg/day is called microalbuminuria and in a patient with diabetes is suggestive of diabetic nephropathy
- Specific assay is required to measure albumin in this concentration
- Albumin excretion > 300 mg per day can be easily picked up by routine laboratory tests and does not require special assay