Pediatric Nephrotic Syndrome

Ashraf Beharrie, M.D.
Pediatric Nephrologist
Salah Foundation Children’s Hospital
Broward Health Medical Center

Objectives

- Describe the etiology of pediatric nephrotic syndrome
- Examine recent developments in the pathophysiology of pediatric nephrotic syndrome
- Recognize atypical presentations and indications for referral to a pediatric nephrologist
- Appreciating the complexity of the glomerular basement membrane
Objectives

Upon completion of this presentation, participants should better be able to:
- Define criteria for diagnosing NS in children
- Recognize the most common etiologies of NS in children
- Understand common treatment plans
- Be aware of the genetic role in pediatric NS

Definition/Background

Pediatric Nephrotic Syndrome (nephrosis) defined as:
- Nephrotic range proteinuria 40mg/m²/hr
  - ~1gm/m2/day
  - semiquantitative Urine P/C value > 2mg/mg (first morning urine sample)
- Hypoalbuminemia: (serum albumin < 2.5 g/dl)
- Edema: (Anasarca > 10 % increase body weight)
- Nephrotic syndrome:
  - constellation of features due to massive protein loss not a disease itself
  - manifestation of glomerular injury
Etiology

Causes of INS include the following:
- MCNS
- FSGS
- MPGN
- Membranous glomerulonephritis (MGN)
- IgA nephropathy
- Idiopathic crescentic glomerulonephritis

Causes of genetic or congenital nephrotic syndrome include the following:
- Finnish-type congenital nephrotic syndrome (NPHS1, nephrin)
- Denys-Drash syndrome (WT1)
- Frasier syndrome (WT1)
- Diffuse mesangial sclerosis (WT1, PLCE1)
- Autosomal recessive, familial FSGS (NPHS2, podocin)
- Autosomal dominant, familial FSGS (ACTN4, α-actinin-4; TRPC6)
- Nail-patella syndrome (LMX1B)
- Pierson syndrome (LAMB2)
- Schimke immuno-osseous dysplasia (SMARCAL1)
- Galloway-Mowat syndrome
- Oculocerebrorenal (Lowe) syndrome

Infections that can cause secondary nephrotic syndrome include the following:
- Congenital syphilis, toxoplasmosis, cytomegalovirus, rubella
- Hepatitis B and C
- HIV/acquired immunodeficiency syndrome (AIDS)
- Malaria

Drugs that can cause secondary nephrotic syndrome include the following:
- Penicillamine
- Gold
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Interferon
- Mercury
- Heroin
- Pamidronate
- Lithium
Etiology (cont’d.)

- Systemic diseases that can cause secondary nephrotic syndrome include the following:
  - Systemic lupus erythematosus
  - Malignancy - Lymphoma, leukemia
  - Vasculitis - Wegener granulomatosis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyangiitis, Henoch-Schönlein purpura (HSP)
  - Immune-complex–mediated - Poststreptococcal glomerulonephritis
Classification of glomerular disease

Primary / Idiopathic Nephrotic Syndrome

- Usually intrinsic kidney disease without systemic causes
- Based on histopathology
  - MCD
  - FSGS
  - MN
  - MPGN
  - Diffuse mesangial proliferation

Secondary Nephrotic Syndrome

- Usually refers to systemic etiology extrinsic to the kidneys
  - SLE
  - HIV
  - Syphilis
  - Hepatitis B, C
  - Henoch-Schonlein purpura
  - Malignancy
  - Drugs
  - Vasculitis
Classification

Genetic abnormalities

- Infantile NS (present < 3 months of age)
- Congenital NS (present 4-12 months of age)
- Associated defects/mutations:
  - Nephrin gene (NPHS1)
  - Wilms tumour suppressor gene (WT1)
  - Podocin gene (NPHS2) familial AR FSGS
  - Alpha actinin 4 gene (ACTN-4)
  - TRPC6 gene - familial AD FSGS
  - Myosin heavy chain 9 (MYH-9) — FSGS African-Americans

Clinical responses:

- Steroid sensitive nephrotic syndrome (SSNS)
- Steroid resistant nephrotic syndrome (SRNS)

Landmark study childhood nephrosis (ISKDC)

- Vast majority preadolescent INS had MCNS
- 90% respond to steroid
- FSGS biopsy proven — only 10-20% steroid responder
- Response to steroid is the prognosticator, regardless of histopathology
Nephrotic Syndrome

Typical Features are likely steroid responders and likely MCD

Atypical Features likely steroid resistant and likely FSGS

<table>
<thead>
<tr>
<th>Nephrosis Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Features</td>
</tr>
<tr>
<td>Age 1-10 years</td>
</tr>
<tr>
<td>Hypertensive</td>
</tr>
<tr>
<td>Normal Renal Function</td>
</tr>
<tr>
<td>+/- microscopic hematuria</td>
</tr>
<tr>
<td>Atypical Features</td>
</tr>
<tr>
<td>&lt;1 yrs, &gt; 10yrs</td>
</tr>
<tr>
<td>Hypertensive</td>
</tr>
<tr>
<td>Elevated Creatinine</td>
</tr>
</tbody>
</table>

Epidemiology

- USA – Annual incidence rate 2-7 cases per 100,000 < 16 yrs
  - Prevalence rate 16 case per 100,000
- ISKDC – 76% children MCNS
  - 7% children FSGS
- Black and Hispanic children at increased risks for SRNS/FSGS
- Asian Children has increased incidence INS x 6 fold compared with European children
- Children < 8 years – Male:Female 2:1
- Older children male = female
- MCNS 70% < 5yrs old
- MCNS 20-30% in adolescents
Pathophysiology

- Initiating event that produces proteinuria remains unknown
- INS believed to have immune pathogenesis
- Studies show abnormal T-Cell subset regulation and expression of circulating permeability factor

- Indirect evidence of immune mediated INS
  - Corticosteroids/ alkaling agents causes remission
  - Nephrotic syndrome remits during measles infection, which suppresses cell mediated immunity
  - Circulating factor-rapid development of proteinuria in transplanted kidney improvement after plasmapheresis
  - Experimental induction of proteinurea in animals by plasma from patient with INS

Pathophysiology

- Various cytokines implicated
  - Interleukins IL-2, IL-4, IL-12, IL-13
  - Interferon gamma
  - Tumor growth factor (TGF-Beta)
  - Tumor necrosis factor (TNF-alpha)
  - Vascular permeability factor

- Association of allergic response to NS
  - Bee stings, jellyfish stings, poison ivy, ragweed pollen etc....
    - INS associated 3 to 4 times more likely with;
      - HLA-DR7
      - HLA-B8
      - HLA-B12 (atopy)
**Pathophysiology**

**Recent Developments**
- Podocyte biology now forefront of pathophysiology of NS
- Intercalated podocyte foot process connected 35-45 nm slit diaphragm (integral part GBM)
- Biopsy shows effacement foot processes long thought to be secondary phenomenon
- Theories now shift towards podocyte molecular biology playing primary role in development of proteinuria
- Numerous mutations podocyte genes
  - Slit diaphragm cytoskeleton – NPHS1, NPHS2, TRCP6, ACTN4 and MYH9
  - Glomerular basement membrane- LAMB2
  - Transcription factors – WT1
Edema Formation

- Classic Hypothesis (underfill theory)
- Overfill Hypothesis
- Recent Theory (interstitial inflammation/intrarenal vasoconstriction)
- Combination of all of the above
Edema Formation

Hyperlipidemia

- Increase liver synthesis
- Decrease function of regulatory enzymes
  - Decrease clearance of cholesterol in the periphery
Complications of NS

- Hypovolemia - children usually intravascular depleted
  - Cool periphery, tachycardia
  - Increase hematocrit
  - Hypotension (late)
  - Hypertension (paradoxical)
  - Low FeNa

- Infections – INS at increased risk
  - Low IgG levels (impaired synthesis, ? Urinary loss)
  - Low complements (urinary loss)
  - Decreased opsonization of capsulated organisms
  - Impaired T-Cell function
  - Drugs such as corticosteroids/ cyclophosphamide suppress immune system
  - Peritonitis/sepsis are most serious and not that uncommon (2-6%)- Pneumococcus, E.Coli
  - Other infections such as meningitis, cellulitis and viral infections
  - Varicella of concern- Can be lethal in the immunosuppressed- treatment with
    Acyclovir and Post exposure prophylaxis with VZIG
  - Routine Childhood vaccination for varicella and pneumococcus has helped

Complications of NS

- Thrombosis- 2-5% of cases
  - Worse in membranous nephropathy (greater protein loss)
  - Renal vein thrombosis, deep vein thrombosis, cerebral sinus thrombosis, pulmonary embolism.
  - Arterial thrombosis less common
  - Imbalance in procoagulation/ anticoagulation factors
Complications of NS

- Acute renal failure
  - Rare complication - ~1% of cases

<table>
<thead>
<tr>
<th>Acute renal failure in nephrotic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prerenal failure due to volume depletion</td>
</tr>
<tr>
<td>Acute tubular necrosis due to volume depletion and/or sepsis</td>
</tr>
<tr>
<td>Intrarenal edema</td>
</tr>
<tr>
<td>Renal vein thrombosis</td>
</tr>
<tr>
<td>Transformation of underlying glomerular disease, e.g., crescentic nephritis superimposed on membranous nephropathy</td>
</tr>
<tr>
<td>Adverse effects of drug therapy</td>
</tr>
<tr>
<td>Acute allergic interstitial nephritis secondary to various drugs, including diuretics</td>
</tr>
<tr>
<td>Hemodynamic response to nonsteroidal anti-inflammatory drugs and angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs)</td>
</tr>
</tbody>
</table>
Initial Investigations

- Do all the following tests in new onset nephrotics
  - CBC, CMP, C3, C4, Lipid Profile, ASO titer, ANA, HIV, RPR, Hepatitis B, C profile
  - Urinalysis, urine electrolytes
  - 24 hr urine collection for protein/creatinine, or early am urine for P/C ratio
  - Renal ultrasound
  - PPD to be placed
  - Check on varicella status
  - Referral to pediatric nephrologist for atypical presentation
    - age <1 yr or > 10 to 12 yrs, persistent hypertension, macroscopic hematuria, low complements, or failure to respond to steroids within 4 weeks

Patient Education

Soon after NS is diagnosed patient and family should be educated about the disease, it's management, and expected course. Family should participate in therapeutic decisions, and encourage to adhere to medical regimen.

Psychosocial issues to be addressed
- Behavior
- Adherence to medication
- Adequate parental/caretaker supervision
- Medical insurance
- Missed work and school due to hospitalization and outpatient visits
- Social worker may be needed
**Terminology**

- Steroid responder - patient goes into remission on prednisolone usually within 10-14 days (trace or negative proteinuria for three consecutive days)
- Steroid resistance - after 4 weeks of prednisolone, patient persists with proteinuria
- Relapse nephrosis - > 2+ proteinuria on 3 consecutive days
- Frequent relapser - 2 or more relapse in the first 6 months of presentation or 4 or more relapse within any 12 months
- Steroid dependency - relapse during the tapering phase of prednisolone or less than 2 weeks after stopping prednisolone
- Late responder - patient goes into remission at about 4 weeks of prednisolone
- Late nonresponder – patient who initially went into remission on steroid but became resistant at a later date

**Treatment**

- For typical features prednisolone is the first line drug
- For atypical features consider a renal biopsy first
- Prednisolone course 8 weeks vs 12 weeks
- Use Ranitidine for the entire steroid course and use calcium carbonate and vitamin D supplement
- Side effects of steroids should be discussed
- Albumin - indications, include clinical hypovolemia and symptomatic edema
- No added salt diet
- Fluid restriction ~1 liter per day
- Penicillin prophylaxis - no consensus
- Vaccinations
  - Pneumococcal polysaccharide vaccine, varicella vaccine

See algorithm
Relapsing NS

- 70-80% of children of steroid responders will have one or more relapse
- Treatment-prednisolone 60mg/m²/per day, until trace or negative proteinuria for 3 days
- Taper treatment 40mg/m²/q other day for 4 weeks, and wean off over another 4 weeks
- Can also use low-dose alternate day prednisolone 10-15mg qod x 6 months
Relapsing NS

- Other meds
  - Levamisole is beneficial for occasional relapses/steroid dependency. Check for neutropenia
  - Cyclophosphamide/ Chlorambucil- useful for frequent relapser, steroid sensitive patients. Usually, 8-12 week course. Monitor for neutropenia and small risk of gonadol toxicity and malignancy
  - Cyclosporine- third line drug for steroid sensitive frequent relapser or in steroid resistant post biopsy. The dose is 5 mg/ kg/ day x 1 year. Aim for a trough 70-150. Be aware of the side effects eg. Hypertension, decreased renal function
  - Mycophenolate mofetal (MMF) – Third or Fourth line drug for both steroid sensitive frequent relapser or steroid resistant ( FSGS). Dose 600mg/m²/day. Side effects include gastritis and leucopenia

Prognosis

- NS is usually a chronic relapsing disease with some degree of morbidity
  - Hospitalization, medication side effects, relapses, and potential progression to ESRD.
  - Since introduction of corticosteroids, INS mortality has decreased dramatically from >50% to ~2%
  - Prognosis varies depending on steroid sensitive vs. steroid resistant.
Steroid sensitive nephrotic syndrome (SSNS)

- Good prognosis
- 93% of responders to steroids will have MCD
- 75% who did not respond will have a histopathology other than MCD
- Despite favorable progress- relapse is the rule
- Longer initial course of steroids 12 week vs. 8 week decreases subsequent relapse by 36%
- Length of time between steroid treatment and remission is early prognostic indicator

Most SSNS will eventually achieve long term remission

- Percent of patients free of relapse
  - 44% 1 year after diagnosis
  - 69% 5 years after diagnosis
  - 84% 10 years after diagnosis

- Overall 90% of children achieve long term remission by puberty
  - Some studies show 20-30% can relapse into adulthood
Prognosis

- Steroid resistant nephrotic syndrome (SRNS)
  - 10% of INS do not respond to steroids
  - Only 2% of MCNS do not respond
  - 1-3% initial responders to steroids, evolve to late non-responder
  - Nonresponders usually have FSGS
  - More than 60% of NS/FSGS who fail to achieve remission, progress to ESRD
  - In contrast, FSGS who achieve remission, only 15% progress to ESRD
  - Even steroid resistant INS have a relative good prognosis if remission can be achieved with a second/third line

Conclusion

- Learning Points
  - Definition of Nephrotic proteinuria in children:
    - 1g/m²/day
  - Common etiologies INS:
    - MCD, Mesangial Hyperplasia, FSGS
  - Treatment Regimens:
    - New-Onset: 60mg/m²/day for 4 weeks and 40mg/m²/qoc for 4 more weeks
    - Common side effects of steroids: HTN, hyperactivity, Obesity
Conclusion

- Learning points (cont’d)
  - Common Complications:
    - Infections: i.e. SBP
    - Hyperlipidemia with risk of cardiovascular disease
    - Thrombosis
    - Psychosocial stress on family and patient

References

References