

Nephrotic Syndrome in Children

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Learning outcomes

- At the end of this lectures the students should be able to
 1. Define nephrotic syndrome
 2. Investigate cause of nephrotic syndrome
 3. Treat idiopathic nephrotic syndrome with steroids.
 4. Prescribe supportive treatment for nephrotic syndrome
 5. Explain the criteria for referring patient to higher level facility

Rare disease, but why is it important?

- Major cause of referral
- Chronic condition
- Complexity in evaluation
- Complexity in management

Definition

- Manifestation of a glomerular disease :
 - Heavy proteinuria $>50\text{mg/kg/24hours}$
 $>1\text{g/m}^2/24\text{hrs}$
or $>40\text{mg/m}^2/\text{hr}$
or urine protein: creatinine ratio
 $>200\text{mg/mmol}$
 - Hypoalbuminemia $<25\text{g/l}$
 - Edema

The key component is proteinuria which is due to disorder of glomerular permselectivity. All other components are secondary to the protein leakage in the urine

Proteinuria

- Dipstick proteinuria 3+ or 4+ need to be quantified.
- Urinary dipstick false +ve in very alkaline urine pH>8.0 and conc urine SG>1.025
- Timed urine specimen. How??
 - 24 hr urine specimen, overnight timed urine specimen
 - Spot urine- first morning urine specimen

Aetiology

- May be due a primary kidney disease
- Or secondary to a systemic disease

Infections

- ✓ Streptococcus, group A β -hemolytic
- ✓ Hepatitis B, C
- ✓ HIV

..aetiology

Systemic disease

- Connective tissue diseases---SLE
- Malignancies – Hodgkin's disease

Drugs ---Heavy metal poisoning– mercury

There is need to rule the possible causes before labling the disease as idiopathic nephrotic syndrome, good history and physical exam and relevant labs inve.

Pathogenesis

- Imbalance of T helper responses,
- Impaired T regulatory function.
- Recently abnormality in B-cell immunity

Pathophysiology of glomerular leakage of protein

- **size selective barrier** :Plasma protein larger than 70kDa restricted from passing thro GBM by a charge –.
- **Charge selective barrier:** Polyanionic glycosaminoglycans, eg heparan sulfate in the GBM restrict the passage of small polyanionic plasma proteins (70-150 kd)-albumin.
 - There is loss of charge selectivity in MCGN
- Increase in GBM permeability : In patients with FSGS a **plasma factor (in few cases)** , Savin factor, produced by lymphocytes increase GBM permeability.

Is proteinuria harmful? (1)

- Causes hypoalbuminemia –lowers plasma oncotic pressure—ECF seep out of the intravascular compartment → hypovolemia → stimulation of RAAS → enhance distal renal tubular sodium reabsorption → oedema.
 - In severe cases hypoalbuminemia can cause hypovolemia with prerenal failure
- Causes loss of small sized proteins in the urine---
 - immunoglobulins –low IgG levels, loss of factor B– alternate pathway of complement activation is compromised → low immunity to infections.
 - Loss of thyroxine binding proteins, 25 OH cholecalciferol-binding globulin, transferrin,

.....Is protenuria harmful? (2)

- Loss of antithrombin III in urine
 - Fibrinogen is big molecule— not lost in urine— higher levels in serum
 - Thus nephrotic syndrome is a hypercoagulable status. Risk of thrombosis is increased by hyperviscosity of the blood.
- There is increased hepatic synthesis of cholesterol, triglycerides and lipoproteins. And increased urinary loss of HDL
- Long standing protenuria may cause interstitial disease

Odema of nephrotic syndrome

Underfil theory

- Hypoalbuminemia → low oncotic pressure
→(change in Starling equilibrium) ECF leaks from intravascular compartment to interstitial compartment→odema.
- Hypovolemia → RAAS stimulation → Na retention → aggravating odema

Odema of nephrotic syndrome

Overfil theory

- Enhanced Na reabsorption as feature of nephrotic kidney due to intrarenal mechanisms – thus primary sodium retention -→ volume expansion → leakage of excess fluid in the interstitium

Clinical Features

- Edema in the common presentation.
 - Mild (subtle periorbital, labia/scrotal)
 - Moderate (peripheral limbs and sacral)
 - Severe (gross limb edema, ascites, pleural effusion)
- May present with the following complication .
Look for them !!!!!
 - Hypovolemia
 - Infection (peritonitis, septicemia, cellulitis) —most important cause of death
 - Thrombosis
 - Protein depletion
 - Acute kidney injury

Differential diagnosis

- AGN
- Acute renal failure
- Chronic renal failure
- Kwashiorkor
- Allergic reaction
- Congestive cardiac failure
- Liver disease with hypoalbuminaemia
- Protein losing enteropathy
- Beriberi

Investigations

- Urinalysis and microscopy
 - Proteinuria
 - hematuria in 23% of MCGN(if hematuria must do microscopy)
- Quantification of proteinuria
 - 24 hr urine collection
 - Timed overnight urine collection
 - spot urine

....Investigations

- U/E/cr -Na low-dilutional plus very high levels of lipids. Pcr raised at presentation in 33% of children with MCNS
- Plasma albumin
Adjust Ca^{2+} for hypoalbuminemia by 0.023mmol/l for each 1g/l ↓ in serum albumin below 40g/l
corrected Ca=total Ca(mmol/l) +0.023[40-albumin(g/l)]
- **Jane has serum albumin 15g/l & Ca^{2+} 1.7mmol/l.**
What is the corrected calcium level?

Investigations

- ANA
- Hep B surface antigen
- Hep C antibody
- ASOT
- antiDNase B
- HIV
- Compliment C3

Idiopathic nephrotic syndrome

(term used interchangeably with primary NS)

Results of the investigations should define the disease :

Nephrotic syndrome: albumin <25g/l, urine protein 3+ or 4+ and of nephrotic range.

Idiopathic: No RBC cast in urine, compliments normal all the other results for etiology of the disease should be negative.

Primary Nephrotic syndrome

Histological appearances identified in primary (idiopathic) NS and the steroid responsiveness

Histological appearance	Freq. %	Steroid responsive(%)
MCNS	77	93
FSGS	8	30
DMH	2	55
Mesangiocapillary GN	6	7
Membranous GN	1.3	0

Steroid responsiveness predicts renal histological lesion with considerable accuracy.¹

Histological class is less important than response to steroids

Idiopathic

- Minimal change GN
- Focal segmental glomerulosclerosis

Non- idiopathic

- Secondary
 - Systemic Lupus Erythematosus (SLE),
 - Henoch Schonlein Purpura (HSP),
 - Membranoproliferative Glomerulonephritis (MPGN)
- Membranous nephropathy
- Congenital nephrotic syndrom

Primary Nephrotic syndrome

- If the clinical and laboratory results are not suggestive of other classification other than minimal change nephrotic syndrome steroids are administered. (see Rx notes)
- Primary Nephrotic syndrome is classified further as steroid responsive or steroid resistant. Classified depending on the response to treatment.

	Minimal change	FSGS
Prevalence	80% in children with idiopathic nephrotic syndrome	10% in children with nephrotic idiopathic syndrome
Median age at presentation	2.5 years	6 years
Response to steroids	95%	30%
Risk of progress to renal failure	Rare	If steroid resistant - 50% f/up 10yrs

Indications for kidney biopsy

If clinical features suggest non MCNS or SrestNS

- Macroscopic hematuria
- Microscopic hematuria with RBCs cast on microscopy
- Microscopic hematuria with persistent hypertension
- Low plasma C3
- Renal failure not attributable to hypovolemia
- Onset before 6 months
- Steroid resistance

.....Indications for kidney biopsy

Optional:

- ❖ Onset 6-12 months
- ❖ Persistent hypertension or microscopic hematuria
- ❖ Onset age >12 years.

Management

- Dietary
 - Normal protein diet as per nutritional status of the patient. High protein diet $\uparrow$ protein synthesis but $\rightarrow$ $\uparrow$ albumin excretion rather than plasma albumin
 - Low salt diet. Use of salt during the preparation of food should be avoided in patients with edema. During remission the child can take food with added salt.
 - If obese due to steroids control calorie intake

Management of oedema

Loss of proteinuria produced by prednisolone and the subsequent diuresis usually occurs 7-14 days after initiating treatment in SRespNS . There is need to manage edema before this period:

- ✓ **salt restriction- avoid using cooking salt in the food.**
- ✓ **Furosemide (1-2mg/kg/day as BD dose)
& spironolactone (2mg/kg/day in two divided doses)**

(spironolactone prevents hypokalemia. Should be started as soon as furosemide is commenced provided the patient is not in renal failure. Diuretics should not be given to patient with hypovolemia)

NO THERAPEUTIC TAPPING OF ASCITES

Complications of nephrotic syndrome

- Infection
- hypovolemia
- thrombosis

Common complications which should be managed promptly

- Infections
 - prophylactic a/b Pen V in patients with gross ascites
 - Septicemia or peritonitis
 - 1st generation cephalosporins or cloxacillin or flucloxacillin
 - PLUS
 - 3rd generation cephalosporins
-

Hypovolemia

- Hypovolemia

Albumin Infusion

Indicated if hypovolemia

- ☐ Low BP
- ☐ Oliguria
- ☐ Evidence of renal insufficiency
- ☐ Low urinary sodium 1-2mmol/l

Treatment: Albumin 1g/kg/day(OD or BD) over 4 hrs, give furosemide (1-2mg/kg) 2 hrs after infusion

Hypertension

- BP short time Rx with Nifedipine (0.25-1mg/kg/day as BD dose
- To either may add atenolol 0.5-1mg/kg OD

Supportive care

- Mobilize px
- Psychological support
- Swollen scrotum may be elevated with pillows to enhance fluid removal by gravity

Management of Idiopathic Nephrotic syndrome

- Management of secondary nephrotic syndrome NOT discussed in the presentation.
- Exclude all those patients with clinical and lab features suggestive of other classification other than MCNS

Steroid treatment

- Treatment of initial episode of SSNS for at least 3 months results in fewer children relapsing by 12-24months with benefit up-to 7 months
- The risk of relapse falls by 11% for every month in therapy up-to 7 months → Rx for 6 months reduces the risk to 30-38% compared to 2 months Rx

Steroids

Guideline for Steroid Treatment for the First Nephrotic Illness

1. Prednisolone 60mg/m²/day or 2mg/kg/day
max 80mg/day for 6 WEEKS

ie Max wt 40kg , Max BSA 1.3

80% respond within 14 days

After one month classify nephrotic syndrome

❖ ***steroid responsive nephrotic syndrome***

❖ ***steroid resistant nephrotic syndrome***

Steroids (2)

- Followed by Prednisolone 40mg/m²/day(1.5 mg/kg/d ay) for 6 WEEKS (If SSNS)

Preventing relapse in SSNS during viral URTI

1. Switch from alternate day prednisolone to daily prednisolone for 5 days
2. If SSNS but not on steroids commence daily steroids (0.5mg/kg daily for 5days)

Period of treatment	Dose of prednisolone
First 6 weeks	Prednisolone 60mg/m ² daily for 6 WEEKS (all tabs administered in the morning)
Next 6 weeks (if SSNR)	Prednisolone 40mg/m ² on alternate days 6 WEEKS (all tabs administered in the morning) If viral URTI give daily prednisolone

Outcome

- **Remission** :- urine protein 0/trace for 3days
- **Steroid resistance**: Failure to achieve remission despite of 4 weeks of prednisolone 2mg/kg/day
- **Relapse** :- urine dipstick 2+ or more on three consecutive days
OR protein 3-4+ plus oedema
- **Steroid dependence**:- 2 consecutive relapse while on steroids or while tapering dose or within 14 days of its cessation
- **Frequent relapser**: Two or more relapses within 6 months of the initial response or four or more relapses within any 12 months period

Outcome (2)

- Before antibiotic era- 2/3 of patients died—
reduced to 35% by antibiotic use --- reduced
to 3% by use of steroids (most of the deaths
are due to infection)

Relapse....

Steroid dependent?

Frequent relapser?

Infrequent relapser?

When to treat?

- Up to 25% relapse remit without added treatment.¹
- Therapy can be deferred for up-to 5 days so long as no edema.
- **Deflazacort** may offer an alternative to prednisone for maintaining remission in children with steroid dependent SRNS.

Education to the patients and caretakers

- SSNS Chronic disease but benign disorder
95% of patients respond to steroids BUT 70% of children who initially respond to steroids relapse
Unusual for NS to be active beyond puberty.
- To test for urine protein at home or lab.
- To seek medical help for proteinuria 2+ or more on 3 consecutive days
- Side effects of steroids
- Importance of Vaccination.

➤ During remission vaccinate

Pneumococcal vaccine

Influenza virus vaccine

Typhoid vaccine

Varicella vaccine (2 dose regime is safe and efficacious)

Ensure the child has received second dose of measles vaccine after the routine one at 9 months, can be given as monovalent or trivalent vaccine (MMR), give at 15 months of age or thereafter.

✓ Hepatitis B vaccine – 3 doses

✓ *Hemophilus type b vaccine*

Live attenuated vaccines can be given if the child is on low dose alternate-day prednisolone

- *Live attenuated vaccines should not be given concurrently with alkalyting agents.*

- *Among the vaccines mentioned above **measles, MMR and chicken-pox vaccines** are live attenuated vaccines.*

Indications for alternative treatment

1. Relapse on prednisolone dosage >0.5 mg/kg QOD **plus** one or more of the following:
 - Unacceptable side effects of steroid
 - High risk of toxicity – boys approaching puberty, DM
 - Unusually severe relapses
 - Inadequate facilities for follow-up or poor compliance
2. Relapse on prednisolone dosage >1 mg/kg QOD

Treatment for steroid dependent

- Minimal Change GN usually respond to steroids, however, up to 50% of MCNS patients develop frequently relapsing nephrotic syndrome.
- Immunosuppressive treatment used include
 - cyclophosphamide,
 - cyclosporine (CyA),
 - mycophenolate mofetil (MMF)
 - Rituximab (RTX) -monoclonal antibody inhibiting CD20-mediated B-cell proliferation and differentiation
 - *In view of benign nature of illness permanent iatrogenic sequel are matters of considerable concern. Benefits should outweigh the harm.*

Who should be referred to a Nephrologist?

- Uncommon condition – early referral to a nephrologist.
- Primary doctor uncertain about management of NS
- Steroid resistant NS
- Frequent relapsers
- Steroid dependent , relapse on prednisolone $>1\text{mg/kg}$ QOD
- History on unusually severe relapse; ARF, severe sepsis
- Patients with indications for renal biopsy
- Patients with indications for alternative treatment

Questions ?

Summary

- Make correct diagnosis of nephrotic syndrome
- Determine if secondary or idiopathic
- If idiopathic treat with prednisolone for 3 months
- Refer if necessary