

This is the Lecture of Nephrotic Syndrome taken by our teacher Dr. Shahabuddin Mahmud Assistant Professor, Paediatric Nephrology in Rajshahi Medical College. It contains some definitions, cause, Pathophysiology, Structural arrangements, clinical features, treatment options etc. This is mostly suitable for the Medical students to prepare their lessons. I have also included the PDF download link of the Power point presentation. I also believe that this document will help the teachers to arrange the Lectures. If you want to include any information's here, feel free to write me.

Today's lecture is about Nephrotic Syndrome (NS). NS and Acute Glomerulonephritis (AGN) are closely related.

**Proteinuria :** Passage of protein in the urine. Normal subject usually excrete about 40-80mg of protein per day ( max. up to 150mg/day).

**Composition of U. Protein-** (1)Albumin (less than 20mg/day) (2) Tamm-Horsfall mucoprotein (30-50mg/day)

**Abnormal Proteinuria:** Proteinuria of 4-40mg/m<sup>2</sup>/hr

**Nephrotic range Proteinuria:** Proteinuria of >40mg/m<sup>2</sup>/hr

**Definition of Nephrotic Syndrome (NS)** · NS is characterized by heavy proteinuria, hypoproteinemia, generalized edema and hyperlipidemia.

**Heavy proteinuria-** when urinary protein excretion more than 40mg/m<sup>2</sup>/hour or 1g/m<sup>2</sup>/24hours.

**Hypoproteinemia-** serum albumin <2.5g/dl.

**Hyperlipidemia-**serum cholesterol>250mg/dl.

### **Incidence of Nephrotic Syndrome (NS)**

- NS is a common disease all over the world
- Overall incidence is reported to be 2040/million population
- In USA & in Europe, the incidence is 1013/million children under 16 years of age.
- In the Indian subcontinent the incidence is estimated as 90-100/million population

### **The Main 4 Criteria of**

#### **Nephrotic syndrome**

1. Massive proteinuria
2. Hypoalbuminemia
3. Edema
4. Hyperlipidemia

## **Nephritic syndrome:**

1. Hematuria
2. Oliguria
3. Azotemia
4. Hypertension

### *Glomerular capillary structure:*

The glomerular capillary wall consists of three layers fenestrated endothelial layer, a basement membrane and an epithelial layer.

The GBM consists of a central electron dense layer, lamina densa and two adjacent layers lamina rara interna & externa.

GBM acts as a semi permeable filter preventing the passage of macromolecules allowing fluids and low molecular weight solutes. The passage of molecules with a diameter of more than 4.5 nm is blocked.

### **GBM-epithelial layer:**

Podocytes of the epithelial cells have an important role in the normal functioning of the glomerular slit membrane.

A number of proteins identified on this podocytes critical for the integrity of glomerular filter, eg, Podocin, Nephrin, Synaptopodin, Alpha-actin 4,P-cadherin.

Gene mutation affecting some of the proteins may result in hereditary nephropathies.

## **Types and Causes of Nephrotic Syndrome:**

**Primary 95%.** It is idiopathic and most common.

1. Pure MCD/Minimal Change Nephrotic Syndrome (MCNS) – 76.4%
2. MCD with mesangial proliferation 2.3%
3. Focal segmental glomerulosclerosis 6.9%
4. Membranoproliferative GN 7.5%
5. Membranous nephropathy 1.5%
6. Others 5.4%

### **Secondary 3-5%**

1. Infections: HBV, HCV, Malaria, HIV, Syphilis
2. Drugs: NSAID, Penicillamine
3. Systemic disease: SLE
4. Malignancy: Leukaemia, Lymphoma

## Important definitions:

**Remission** - Protein free urine ( $<4\text{mg/m}^2/\text{h}$ ) for 3 consecutive days.

**Relapse** - proteinuria 3+ or more for 3 consecutive days, after having been in remission

**Frequent Relapse** - A Relapser who has 2 or more relapse within 6 months of the initial episode or more than 3 relapses within any 12 months period.

**Infrequent Relapser** - a responder who relapses but 3 or less relapses within one year.

**Steroid dependent** - Occurrence of 2 consecutive relapses during alternate day prednisolone therapy or within 2 wks. of its discontinuation.

**Steroid resistant**- Failure to achieve remission following 8 week' Prednisolone  $60\text{mg/m}^2$ .

## *Pathogenesis of Minimal Change Nephrotic Syndrome:*

Immunologic mechanism may be involved in the pathogenesis of MCNS. T-cell activation might led to the production of a cytokine that may affect the filtration of proteins by the glomerular capillaries, by interfering with the polyanionic charge or through some other undefined mechanism.

## *Several study results regarding pathogenesis of MCNS has been shown:*

1. Diminished cellular immunity
2. Low IgG
3. Abnormalities of T-lymphocytes cell subsets.
4. Increase serum level of soluble IL-2 receptor, IL-8, TNF
5. Vascular permeability factor
6. Up regulation of the gene for IL-4 and IL-13 in peripheral blood lymphocyte and glomeruli

## *Pathophysiology of Glomerular Leakage of Protein*

The size-selective barrier, which is thought to consist of pores in the glomerular-basementmembrane meshwork, restricts the passage of larger plasma proteins (more than 150 kd).

Investigations have revealed that the defect in minimal-change glomerulopathy results mainly from a loss of charge selectivity, whereas the defect in membranous glomerulonephritis results mainly from a loss of size selectivity.

## *Hyperlipidemia*

HMG co reductase in liver limits the biosynthesis of cholesterol. Hyperlipidemia is related to the severity of proteinuria and hypoalbuminemia. In NS, hypoalbuminemia causes Up regulation of HMG co reductase. Down regulation of lipoprotein lipase, VLDL receptor and hepatic triglyceride lipase. There is increased production of all lipids and decrease in receptor mediated removal of lipoprotein and lipoprotein lipase.

**Treatment:** Dietary modification, HMG co reductase inhibitor (atrovastatin, simvastatin etc)

## **Clinical Feature of Minimal Change Nephrotic Syndrome:**

- Onset of MCNS is between 2-6years.
- Onset beyond 8 years associated with significant glomerular injury.
- More in boys 60-70%.
- Insidious onset, with puffiness, gradual involvement of extremities and abdomen, if untreated may become massive

### **Clinical evaluation:**

- The child should be examined to detect any associated infection.
- In MCNS, BP is usually normal. With massive edema it may be elevated. Hypovolemia stimulates several vasoconstricting mechanisms that lead to HTN.
- Features of systemic disorder should be looked for like- fever, rash, joint pain, hepatosplenomegaly and lymphadenopathy.
- Associated ARI is common.
- Mild diarrhoea is not uncommon, probably due to intestinal edema.
- Occasionally generalized swelling may develop acutely and be associated with gross haematuria.

On Previous Post we discussed about some Important definitions, Clinical features, Pathophysiology, Types, Causes etc. In this part of lecture we are going to deals with the Necessary Investigations, Indication for renal biopsy in NS, Specific and Supportive treatment, Complications, Causes of susceptibility to infection in MCNS, Some Conditions Associated with Nephrotic Syndrome with their presentation, responsible organisms and treatment. As the treatment is done with Steroid, there are some adverse effects of using Steroid. The possible outcome also vary in some extent depending upon the steroid dependency.

Some problem based questions and Download link is given below. See here the [first part of Nephrotic Syndrome lecture](#).

## **Investigations for Nephrotic Syndrome:**

### **Urinalysis:**

1. 3+ to 4+proteinuria by heat coagulation test or dipstic test.
2. 24 hours UTP is the `Gold-standard' but not essential for young children. Spot urinary Protein : Creatinine >2 is suggestive of nephrotic range of proteinuria.
3. Presence of persistent microscopic haematuria suggests the likely hood of significant renal histological lesion.
4. Urine culture to exclude UTI.

## **Proteinuria**

1. Selective P-consisting mainly of albumin.
2. Non selective P - containing significant amount of proteins. higher molecular wt. of (Transferrin & IgG)
3. U.P transferrin /U.P albumin= < 0.1 highly selective, >0.2 nonselective, moderately selective. 0.1-0.2

## **Blood :**

1. Serum albumin <2.5g/dl.
2. STP low with altered A:G ratio.
3. Serum cholesterol/Lipid profile TC,LDL,VLDL are increased. HDL normal. ionized Ca is normal.
4. Calcium - total Ca is reduced but Blood- cont.
5. Blood urea & serum creatinine are usually normal in MCNS.
6. Serum electrolytes hyponatraemia. occasional
7. Complement: C3,C4 normal
8. Serum IgG reduced, IgM raised.
9. Hepatitis B serology, AntiHCV,
10. CBC, Blood grouping.

## **Other investigations:**

1. USS KUB
2. CXR
3. Renal biopsy. It is not needed usually except in below situation

## **Indication for renal biopsy in Nephrotic Syndrome:**

### **At onset**

1. Age <1yr or >16 yrs.
2. Persistent macro/microscopic haematuria
3. Low C3 level
4. Sustained HTN
5. Impaired RFT, not attributable to iv hypovolemia
6. Presence of extrarenal features; arthritis, rash, lymphadenopathy.

### **After initial therapy**

1. Steroid resistance initial or late
2. Before starting treatment with Cyclosporin A

# Management of MCNS

## Specific treatment:

### Treatment of initial episode (ISKDC/Modified)-

Oral prednisolone 60mg/m<sup>2</sup>/day(or 2mg/kg/day) daily in 2-3 divided doses for 6weeks, followed by 40mg/m<sup>2</sup>/day(or1.5mg/kg/day) as a single morning dose on alternate day for 6 weeks.

### Prolong initial treatment results longer remission and fewer relapses.

A meta analysis published by an Australian group- shows that children in their first episode should be treated for at least 6 months.

First 2 month of which are according to the ISKDC regimen.

In month 3-6 - alternate day treatment , the dose being reduced by 25% every 4 weeks.

[Ref. Hodson et al.Arch Dis Child 2000;83:45-51.]

Subsequent courses Relapses are treated with oral prednisolone 60mg/m<sup>2</sup>/day daily in 2-3 divided doses until the urine become protein free for 3 consecutive days, followed by 40mg/m<sup>2</sup>/day as a single morning dose on alternate day for 4 weeks.

**General care:** General care should strictly maintain.

1. Diet- a balanced diet consisting of 1.52g/kg/day of proteins & adequate calorie for age is recommended.
2. Fat should constitute no more than 30% of total calories.
3. Complex carbohydrates are preferred over simple sugars.
4. Salt restriction(2mmol/kg/day) with avoidance of salted snacks in edematous HTN pts.
5. Drugs: Furosemide with or without Spironolactone may be tried. Oral Penicillin 25-40 Mg/Kg/Day sometimes given.

## Complications of Nephrotic Syndrome:

1. Infections: Cellulitis, peritonitis, UTI, pneumonia, meningitis, pyogenic infection of bone and joints, T. varicella, measles, fungal infection.
2. Hypovolemia
3. Thromboembolism
4. Hyperlipidemia
5. Acute renal failure
6. Hyper lipidemia
7. Malnutrition

## Factors predisposing to thrombosis in MCNS

1. Thrombocytosis
2. Increase platelet aggregability
3. Increased plasma concentration of clotting factors: factor V, VII, VIII, X, fibrinogen.
4. Accelerated thromboplastin generation
5. Reduced antithrombin III
6. Hypovolemia
7. Corticosteroid therapy

## Causes of susceptibility to infection in MCNS

1. Low plasma IgG
2. Low serum factor B
3. Impaired opsonization
4. Impaired lymphocyte transformation
5. Drug induced immunosuppression

## Some Conditions Associated with Nephrotic Syndrome:

### Peritonitis

1. Presentation—abdominal pain, diarrhoea, vomiting.
2. Organisms—Pneumococci, E. coli, H. influenzae.
3. Treatment— iv ceftriaxone/cefotaxime/ampicillin with aminoglycoside for 10-14 days.

### Pneumonia

1. Presentation—Fever, tachypnoea, cough.
2. Organisms— Pneumococci, H. influenzae.
3. Treatment— oral amoxicillin/Cephalexin/Amoxiclavlor Ampicillin with aminoglycoside for 7-10 days in severe infections.

### Cellulitis

1. Presentation—Redness, tenderness or induration.
2. Organisms— Beta haemolytic streptococci, Pneumococci, H. influenzae, staphylococci.
3. Treatment— I/V cloxacillin with ceftriaxone till resolution of indurations followed by oral cloxacillin and cefixime for 10 days.

### UTI

1. Presentations—usually asymptomatic, non response to steroid, occasional fever, dysuria.
2. Organisms: Gram-ve E.coli, pseudomonas, klebsiella.
3. Treatment— iv antibiotic(combination) according to culture sensitivity 7-10 days. Withdraw of steroid unless f/up c/s is sterile.

## **Fungal infections**

1. Presentation- pulmonary infiltrate, persistent fever, unresponsiveness to antibiotics, sputum or urine shows septate hyphae.
2. Organisms-Candida, Aspergillus spp.
3. Treatment: Skin mucosa-Fluconazole for 10-14 days and Systemic- Amphotericin B for 14-21days.

## **Adverse effects of steroid**

Cushingoid feature, Acne, Hirsutism, HTN, Sub capsular cataract, Osteopenia, Avascular necrosis, Glycosuria, Short stature, Suppressed adrenal activity, Immunocompromised state and prone to infection.

## **Outcome in Nephrotic Syndrome:**

### **Steroid Sensitive NS:**

1. The ultimate outcome in MCNS is excellent with most children getting completely cured by the age of 10-15 yrs.
2. In a given patient, it is not possible to predict the course or the age at which cure might take place.
3. The family should be encouraged to focus on the general well being, growth & development and schooling of the child.
4. Unnecessary restriction on diet and activity must not be imposed.

33% ---suffers from only one attack. stopping the corticosteroid treatment and a cure takes place usually after 3 or 4 episodes, which responds to standard course of corticosteroid.

10-20% --- experience relapse after

40-50% --- experience frequent relapse.

### **Steroid Resistant NS:**

1. Steroid resistant NS is difficult to treat, the long term prognosis is often poor.
2. In children with FSGS, a trial may be given with I.V. Methylprednisolone, and oral cyclophosphamide. Cyclosporine may also be used.
3. ACE Inhibitors and ARB may be used to reduce the intensity of proteinuria.
4. Hypertension should be strictly controlled.

## **Problem Based Questions:**

Q1: A 5 year old boy admitted with swelling of whole body and scanty micturation for 15 days. His blood pressure was 90/60 mmHg and bedside urine albumin was 4+. What is your diagnosis and Treatment?

Q2: A 7 years old child presented with scanty micturation, generalised edema with ascities and proteinurea. What is your diagnosis?

Q3: A 5 years old boy child presented with puffy eyelid and face for 3 days, passing less urine for 3 days. Recentlr he had a cold with fever, he has no hematuria and his blodd pressure is normal. What is your diagnosis?

Ans: Diagnosis: NS with Respiratory Tract Infections.

