Nephrotic syndrome

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Nephrotic syndrome

Introduction

- Chronic illness
- Recurring disease – Relapses and remissions
- Usually grow out of the disease after 12 years
- Most likely aetiology is minimal change nephrotic syndrome
- Risk of end stage renal disease – rare

Definition

- Oedema
- Hypoalbuminaemia (s. albumin <25g/l)
- Gross proteinuria (nephrotic range)
  urine protein/creatinine ratio
  >200mg/mmol or
  3+ protein on urine dipstick or
  proteinuria ≥ 300mg/dl

Hyperlipidaemia (Cholesterol > 200mg/dl)

Remission

Urine albumin nil/trace (<4mg/m^2/hr) for 3 consecutive early morning specimens

or

Urine protein creatinine ratio <20mg/mmol

Relapse

- urine albumin $\geq 3+$ ($40 mg/m^2/hr$) on three consecutive early morning specimens, having been in remission previously

or

- Urine protein creatinine ratio $\geq 200 mg/mmol$

Frequent relapsing

Two or more relapses during first 6 months after the initial episode or 4 or more relapses in any 12 months

Response to steroids

Steroid responsive

Remission achieved within initial 4 weeks of high dose daily steroid therapy

Steroid dependent

Two consecutive relapses while on alternate day steroids or within 14 days after cessation of steroids

Steroid resistance

Failure to achieve remission within 4 weeks of therapy with daily prednisolone (60mg/m2/d)

Classification

- **Primary (Idiopathic)** – most common
- **Secondary** – secondary to systemic disorders, or following drugs and heavy metals
  - (SLE, HSP, Vasculitis, lymphoma, leukemia)
  - (infections – Hepatitis B,C, HIV, leprosy, IMN, syphilis)
  - (captopril, penicillamine, gold, NSAIDS)
- **Congenital** – manifesting at birth or within first 3 months of life.
  - poor prognosis

Primary (Idiopathic) nephrotic syndrome

- 90% of children with nephrotic syndrome
- Cause remains unknown, seen more commonly in atopic families

Histologic types:

Minimal change NS 85% - >**95% SSNS**

Focal segmental glomerular sclerosis (FSGN) 5%– **20% SSNS**

Diffuse mesangial proliferation 10% – **50% SSNS**

Membranous nephropathy

Membranoproliferative glomerulonephritis

Pathophysiology

- An increase in glomerular capillary wall permeability leading to gross proteinuria & hypoalbuminaemia
- The cause for the increased permeability is not well understood

Pathophysiology

- In minimal change disease, possible T cell dysfunction leading to alteration of cytokines has been recognised

- This leads to loss of negatively charged glycoproteins within the glomerular capillary wall

Mechanisms of oedema

- Incompletely understood
- Protein loss leads to **hypoalbuminaemia.** This decreases the plasma oncotic pressure leading to transudation of fluid in to extra cellular space
- This leads to reduce intravascular volume

- Reduced intravascular volume decreases renal perfusion pressure. This activates renin angiotensin aldosterone system which stimulates tubular reabsorption of sodium

- Reduced intravascular volume causes release of ADH enhance reabsorption of water

Mechanisms of elevated serum lipid

- Hypoalbuminaemia stimulates generalized hepatic protein synthesis including synthesis of lipoproteins
- Lipid catabolism is diminished because of reduced plasma lipoprotein lipase due to increased urinary loss

Pathology

- In minimal change disease the glomeruli appear normal or show minimal increase in mesangial cells and matrix
- 95% responds to corticosteroid therapy

- Mesangial PGN characterized by a diffuse increase in mesangial cells and matrix on light microscopy
- Immunofluorescent microscopy reveals mesangial deposition of IgM and/or IgA
- 50% respond to corticosteroid therapy

- In FSGS glomeruli shows mesangial proliferations and segmental scarring on light microscopy.
- Immunofluorescent microscopy shows IgM and C3 staining in the areas of segmental sclerosis
- 20% responds to corticosteroid therapy

In clinical practice

- Those who respond to steroid therapy is labeled as having **steroid sensitive nephrotic syndrome**
- Those who respond within 14 days of commencement known as **early responders.**
- Response occurs after 14 days known as **late responders**

Clinical Features

- Incidence is 2-4/100,000
- Male: female = 2:1
- Onset at 2-6 years
- Often a preceding history of URTI

Clinical Features

- Oedema in periorbital area & in the lower extremities, becomes generalized with development of ascites, pleural effusion and genital oedema
- decreased urine output
- Lethargy, irritability, decreased appetite, diarrhoea, abdominal pain, hypertension
- Hypertension and gross haematuria are uncommon

Atypical features suggest non minimal change NS

- Age of onset < 1year or > 8 years
- Macroscopic haematuria/ persistent microscopic haematuria
- Persistent elevated BP
- Evidence of renal impairment
- Persistently reduced complement levels
- Steroid resistance
- Extra renal manifestations (arthritis, rash, anemia, fever)

Differential diagnosis

- Acute post streptococcal glomerulonephritis
- Angioedema
- Congestive heart failure
- Protein loosing enteropathy
- Hepatic failure
- Chronic glomerulonephritis
- Protein malnutrition

Investigations

- **Urine FR** :
  proteinuria ≥ +3, transient haematuria in 20–30%, hyaline casts

- **Urine protein to creatinine ratio** :
  >200mg/mmol

- **Serum proteins :** albumin <25g/l

- **Serum cholesterol and triglyceride**
  levels are elevated

Investigations

- **Renal function** is usually normal
- **C3 & C4 levels** are normal
- **Urine culture** & ABST

Management

Supportive care and monitoring

- Height , weight , body surface area (BSA), BP – on admission
- Weight, Input / output, urine ward test – daily
- BP – three times a day and more frequently if abnormal

Supportive care and monitoring

- Bed rest – not recommended
  activity as tolerated
- Diet – Normal calories
  Normal protein
  (no restriction /no need of high protein)

- No added salt during oedema

- Restriction of fat will be an advantage

Supportive care and monitoring

- Antibiotics –

  In case of infection – treat vigorously

  Severe oedema and free fluids in the abdomen – might need prophylactic antibiotics to prevent spontaneous bacterial peritonitis

  Pneumococci and H. influenzae
  (Encapsulated organisms)

  Associated sepsis should be treated vigorously

Supportive care and monitoring

Fluids – No restriction needed

Should be closely observed for signs of hypervolemia

Diuretics – should be used in severe oedema , but with caution due to risk of hypovolemia

It should be used only after correction of intravascular volume

Furosemide 1-2 mg/kg in divided doses PO/IV

Should be used with 25% salt free albumin / cryo poor plasma. Albumin should be given as a slow infusion

Supportive care

- Hyperlipidaemia – Dietary control of saturated fats will be an advantage
- Lipid lowering drugs are not needed as hyperlipidaemia is transient
- Antihypertensives
  Loop diuretics and calcium channel blockers
- Advice to mother regarding disease & steroids side effects

Specific management – Steroids

Management of first episode

- Induction of remission with high dose daily prednisolone
- Prednisolone 60 mg/m^2/day, daily therapy for 4-6 weeks. 4 weeks for early responders and 6 weeks for late responders
- Maximum 60 mg/ day
- Preferably given as a single dose in the morning
- Should **not** be given on empty stomach
- May be given in divided doses to reduce GI side effects and can be combined with a H_2 receptor blocker

Achieving remission

- 80% of SSNS will do so with in 14 days
- About 80-90% of children respond to steroid therapy within 3 weeks

Maintenance of remission

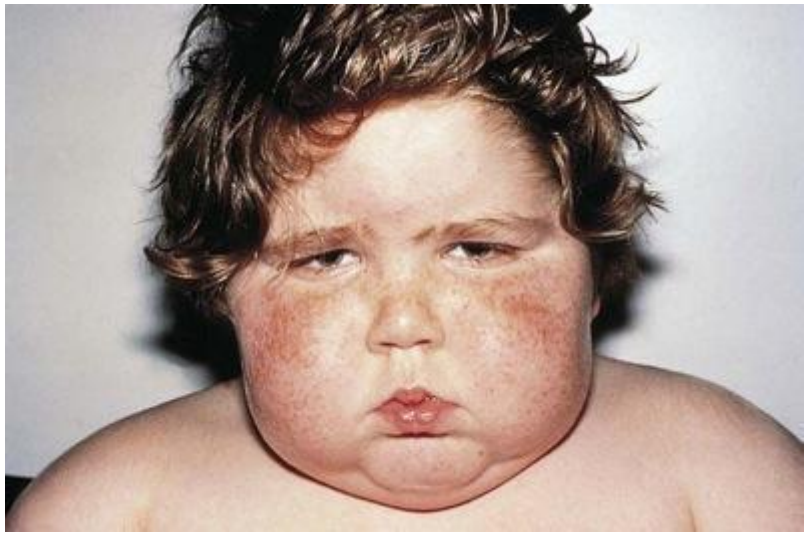
- Prednisolone 40 mg/m^2/day EOD (every other day) for 4 weeks
- Taper it slowly over 3- 6 months, specially in late responders
- Longer tapering regimen will help to maintain the remission
- Studies suggested alternative day steroids for 6 months will reduce the relapse by 33%.

Another regime after high dose of therapy (Polish regime)

- After prednisolone high daily dose i.e. 60 mg/m^2/day 4-6 weeks
- 60 mg/m^2/day EOD for 2 weeks then
- 50 mg/m^2/day EOD for 2 weeks, then
- 40 mg/m^2/day EOD for 2 weeks then
- 30 mg/m^2/day EOD for 2 weeks then taper it altogether for a period of 6 months

Prednisolone

- Wonderful drug if used cautiously
- Precautions and monitoring
- **Cushings facies**



Prednisolone

- **Regular eye checkups**

  Posterior sub capsular cataract, glaucoma, secondary ocular infections

Prednisolone

- **Assessment of growth**

  Height – short stature

  Weight – obesity (weight gain and increased appetite)

- **Hypocalcaemia and osteopenia**

  Regular Dexa scan

  Calcium supp/or bisphosphonates for severe osteopenia

  Regular calcium monitoring

Prednisolone

- **Addisonian crisis**

During stress or surgeries

- Might need IV hydrocortisone up to about 1 year after cessation of steroids

On discharge

- Educate about the illness and compliance
- How to check urine for protein at home
- Diet & exercise
- Vaccination
- When to come back
- Risk of infections
- SE of prednisolone
- Maintain a diary mentioned about proteinuria, medications and intercurrent illness
- During a GP visit indicate the child's clinic book
- Normal activity and school attendance

Immunization – special issues

- Live vaccines are contraindicated during high dose steroid therapy and 3 months after cessation
- All killed vaccines should be offered preferably during EOD therapy
- Hepatitis B should be given and antibody levels should be checked
- Varicella vaccine (Live vaccine) should be given while off prednisolone for past 3 months
- Pneumococcal vaccine
- No live vaccines while on cyclophosphamide or within 6 months after cessation of therapy

Urine for protein at home

- Should be done daily in the morning during a relapse
- In remission – when there is oedema or infection daily
- Otherwise 2-3 times per week

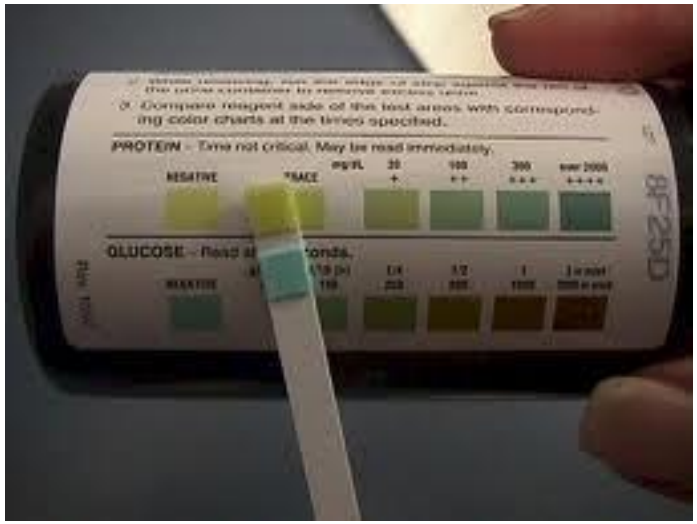
Urine for protein at home

Heat test

- Fill 2/3 of test tube with urine
- should be heated at slant and upper half should be heated up to boiling point
- If there is turbidity add 10% acetic acid or vinegar to exclude phosphates
- Persistent turbidity is read against a black print

Urine for protein at home

- Dipstick test –



Grading of proteinuria

- Nil : No turbidity
- Trace : Slight turbidity , but no difficulty in reading the black print
- + : Clouding of the print, but still readable with difficulty
- ++ : Can notice the black but can not read the print
- +++ : Can not notice black
- ++++: Precipitate

Relapse

- urine albumin ≥3+ (40mg/m2/hr) on three consecutive early morning specimens, having been in remission previously

or

- Urine protein creatinine ratio≥200mg/mmol

Relapse

- Many children experience at least one relapse(70%)
- Usually precipitated by upper viral resspiratory tract or GI infections
- In the past relapse rate is 60 -80% but with longer duration of steroid treatment relapse rate has reduced to 30 -40%
- Look for infections and treat if any
- Can wait for 5-7 days to commence therapy provided the child is free of oedema. Could be an episode of transient proteinuria

- Relapse should be treated with prednisolone 60 mg/m^2/day until urine nil of protein for 3 consecutive days (remission)

- The dose is then changed to 40 mg/m^2/day every other day for 28 days. Then the dose of prednisolone may be tapered over 3-6 months

Frequent relapsing

Two or more relapses during first 6 months after the initial episode or 4 or more within a period of one year

Response to steroids

Steroid responsive

Remission achieved with high dose daily steroid therapy alone

Steroid dependent

two consecutive relapses occurring during steroid therapy (EOD) or within 14 das after cessation of steroids

Steroid resistance

Failure to achieve remission within 4 weeks of high dose daily steroid therapy

Treatment of frequent relapses & steroid dependency

- First line of treatment is maintenance therapy with low dose prednisolone 0.1-0.6mg/kg EOD for 6 months followed by slow tapering.
- If a child requires more than 0.6mg/kg of prednisolone on alternate days to remain protein free, and particularly if there are signs of steroid toxicity then alternative therapy should be considered

Alternative therapy

- Levamisole
- Cyclophosphamide
- Cyclosporine
- Mycophenolate mofetil
- Azathioprine
- Chlorambucil
- Tacrolimus

Levamisole

- Ant-helminthic drug , steroid sparing effect
- Dosage – 2.5 mg/kg/day EOD
- Indications – steroid dependent nephrotic syndrome
- Not to induce remission but to maintain remission
- Initially with EOD prednisolone subsequently as a single agent
- Duration up to 5 years
- SE – Reversible neutropenia – monitor FBC
- Be alert in throat infections – might indicate agranulocytosis
- Drug should be discontinued permanently
- Itchy skin rash & vasculitis – permanent discontinuation
- Other SE – Liver toxicity, Convulsions

Cyclophosphamide

- Indications- to maintain prolong remission and reduces the number of relapses in steroid dependent and frequent relapsing nephrotic syndrome

- PO/IV
- PO- 3 mg/kg once a day for 8 weeks / 2 mg/kg once a day 12 weeks
- IV- 600 mg/m^2 monthly for 6 months

SE:

- Are related to total cumulative dose

- Recommended cumulative dose 168 mg/kg

- Haemorrhagic cystitis – specially with IV
- granulocytopenia , disseminated varicella, pigmentation, hair loss, future malignancy, Nausea, Vomiting, amenorrhoea, azoospermia with high cumulative dose

Cyclophosphamide

Precautions :

- Well hydration of the patient before and after therapy
- Increased oral intake of fluids even with oral therapy
- Monitor FBC before administration of IV
- FBC weekly during oral therapy and monthly during IV therapy
- Discontinue in neutropenia Absolute N Count < 1500

Cyclosporin A

- Recommended as initial therapy for steroid resistant nephrotic syndrome
- Initial dose 3-5 mg/kg/d in 2 devided doses, 2-3 years

Adverse effects of cyclosporin

- **H**ypertrichosis (hirsutism)
- **H**ypertrophy of gums
- **H**epatic dysfunction
- **H**igh/ impaired renal functions
- **H**yperkalemia
- **H**ypertension

Steroid resistant patients

- High dose pulse **methylprednisolone** intravenously
- Methylprednisolone is usually given as a 30mg/kg/day bolus (max 1g) daily for 3 days

- ACE inhibitors and angiotensin II blockers may be helpful as an adjunct therapy to reduce proteinuria in steroid resistant patients

Indications for renal biopsy

- Not regularly done

- Infants <6 months of age
- Steroid resistance
- Before treatment with 3rd line drug
- Clinical course suggesting a non minimal change disease

Complications

- Mortality 1-2%
- Infections eg. Spontaneous bacterial peritonitis, disseminated varicella
- Hypovolaemia
- Thrombosis
- Steroid side effects

Management of hypovolaemia

- Rapid protein loss → hypovolaemia

- **Hypovolaemic crisis:**

  Abdominal pain, cold extremities, prolonged capillary refill time > 2 seconds, wide central:peripheral temperature gap, rapid thready pulse & narrow pulse pressure and hypotension

- **Treatment :** Rapid IV infusion of cryo-poor plasma, salt poor albumin, 25% salt free albumin is the best

Infections

- Respiratory tract infections & primary peritonitis are frequent infections
- UTI can precipitate a relapse or may be a cause for poor response to prednisolone
- Chickenpox & measles could become severe if on prednisolone/cyclophosphamide
- Increase susceptibility to infection is due to
  - Urinary loss of IgG & properdin factor B
  - Defective cell mediated immunity
  - Immunosuppressive therapy
  - Malnutrition
  - Oedema fluids act as a potential culture medium

Thromboembolic events

- Increased risk 2-5%
- Both arterial & venous thrombosis may be seen including renal vein thrombosis, pulmonary embolus, sagittal sinus thrombosis & thrombosis of catheters
- Risk of thrombosis is related to
  - Increased prothrombotic factors (fibrinogen, thrombocytosis, haemoconcentration & relative immobilization)
  - Decreased fibrinolytic factors (urinary loss of antithrombin protein C & S)

Causes of abdominal pain

- Hypovolaemia
- Peritonitis
- UTI
- Gastritis (related to steroids)
- Cellulitis
- Renal vein thrombosis
- Non specific

Prognosis

- Prognosis – depend on the timely, correct management of the initial episode
- Response to steroid therapy is the most important prognostic marker
- Children who respond rapidly to steroids and those who have no relapses during the first 6 months after diagnosis are likely to follow an infrequently relapsing course

Prognosis

- SSNS resolves towards the end of 2nd decade

- SRNS most often caused by FSGS, generally have much poorer prognosis

- They develop progressive renal insufficiency & lead to end stage renal failure

Congenital NS (Finnish type)

- Rare, autosomal recessive
- C.F. within 1st 3 months with persistent oedema and infections
- Additional features – prematurity, large placenta, respiratory distress & skull suture separation.
- Treatment: dialysis & renal transplant otherwise death by 5 years.
- AN diagnosis : Increased alpha feto protein

Secondary NS

Should be suspected in patients

- Age >8 years
- Hypertension
- Haematuria
- Renal dysfunction
- Rashes
- Arthralgia
- Depressed serum complement levels

Causes of secondary NS

- **Other GN** : membranous, MPGN
- SLE, Henoch Schonlein purpura
- **Chronic infections** – P.malaria, Hepatitis B & C, filaria, leprasy & HIV
- **Tumours** – Hodgkin lymphoma
- **Drugs** – penicillamine, captopril, gold, NSAID, mercury probenecid, ethosuximide, methimazole, lithium, procainamide, chlorpropamide, phenytoin


Thank
you