Nephrotic Syndrome

Synonym: nephrosis

Nephrotic syndrome is a clinical syndrome showing specific features of heavy proteinuria causing hypoalbuminaemia or hypoproteinaemia. It is caused by increased permeability of serum protein through the damaged basement membrane in the renal glomerulus. The definition of nephrotic syndrome includes both massive proteinuria (≥3.5 g/day) and hypoalbuminaemia (serum albumin ≤30 g/L)\(^1\).

As a result of massive proteinuria and hypoalbuminaemia, nephrotic syndrome is frequently accompanied by oedema, dyslipidaemia, abnormalities in coagulation/fibrinolysis, reduced renal function, and immunological disorders.

Adult-onset nephrotic syndrome differs from childhood-onset in several important ways. Most importantly, nephrotic syndrome in adults is more aetiologically heterogeneous compared to children and treatment approaches therefore rely more heavily on the histological diagnosis provided by renal biopsy\(^2\).

Epidemiology

- Nephrotic syndrome is a common glomerular disease in children with significant variability in both incidence and steroid responsiveness among various ethnic groups. The average incidence of nephrotic syndrome is 2-16.9 per 100,000 children worldwide\(^3\).
- In adults, diabetes mellitus is the most common secondary cause and focal segmental glomerulosclerosis and membranous nephropathy are the most common primary causes\(^4\).
- Minimal change disease accounts for 10-25% of cases of nephrotic syndrome in adults\(^5\).
- The incidence of minimal change disease is higher in children with a reported incidence of 2 per 100,000 per year in Caucasian children and higher rates in Arabian and Asian children\(^6\).

More common causes of the nephrotic syndrome

It can be caused by a wide range of primary (idiopathic) and secondary glomerular diseases. See also separate Acute Nephritis, Interstitial Nephritides and Nephrotoxins and Glomerulonephritis articles.

Primary glomerular diseases

- Minimal change glomerular disease - the most common cause in children.
- Focal segmental glomerulosclerosis - the most common cause of idiopathic nephrotic syndrome in adults.
- Membranous glomerular disease.
- Membranoproliferative glomerulonephritis - primarily affects children and young adults; presents with nephrotic or nephritic syndrome, or with asymptomatic renal disease\(^7\).

Secondary glomerular diseases\(^8\)

- Infection - eg, HIV, hepatitis B and hepatitis C, mycoplasma, syphilis, malaria, schistosomiasis, filariasis, toxoplasmosis.
- Collagen vascular diseases - eg, systemic lupus erythematosus, rheumatoid arthritis, polyarteritis nodosa, Henoch-Schönlein purpura, vasculitides.
- Metabolic diseases - eg, diabetes mellitus, amyloidosis.
- Inherited disease - eg, Alport's syndrome, hereditary nephritis, sickle cell disease.
- Drugs - eg, non-steroidal anti-inflammatory drugs (NSAIDs), captopril, lithium, gold, diamorphine, interferon alfa, penicillamine, probenecid and many others.
- Toxins - eg, bee sting, snake bites, phytoxins.
- Pregnancy - eg, pre-eclampsia.
- Transplant rejection.

Presentation

Symptoms

- In children, facial swelling is a common presenting feature, with periorbital oedema often being the first evidence that something is wrong; oedema may progress to involve the whole body.
- Adults tend to present with peripheral oedema affecting the ankles and legs, which may progress to involve the whole body.
- Some patients may notice frothiness of their urine.
- Hypercoagulability may manifest as venous or arterial thrombosis - eg, deep vein thrombosis, myocardial infarction.
Recurrent infections and/or general fatigue, lethargy, poor appetite, weakness or episodic abdominal pain may cause presentation to a doctor.

Signs
Clinical signs of nephrotic syndrome include:

- Oedema (oedema of dependent parts or generalised oedema are the main clinical findings): periorbital oedema (facial oedema may be found in children), lower limb oedema, oedema of the genitals, ascites.
- Tiredness.
- Leukonychia.
- Breathlessness: pleural effusion (occasionally, severely hypoalbuminaemic cases may have pleural effusions or ascites), fluid overload (high jugular venous pressure), acute kidney injury.
- Breathlessness with chest pain: pulmonary embolism, myocardial infarction.
- Dyslipidaemia: eruptive xanthomata, xanthelasmata.

Investigations

- Urine dipstick analysis: proteinuria and check for microscopic haematuria.
- Midstream urine for microscopy, culture and sensitivities to exclude urinary tract infection.
- Quantify proteinuria using an early morning urinary protein:creatinine ratio or albumin:creatinine ratio.
- FBC and coagulation screen.
- Renal function tests.
- LFTs (to exclude liver pathology); bone profile (calcium, phosphate, alkaline phosphatase).
- Check for other systemic diseases and causes of nephrotic syndrome:
  - ESR and CRP.
  - Fasting glucose.
  - Immunoglobulins, serum and urine electrophoresis.
  - Autoimmune screen if an underlying autoimmune disease is suspected: autoantibodies and complement levels.
  - Hepatitis B and hepatitis C; HIV.
- CXR and abdominal or renal ultrasound scan (especially if renal function is abnormal): to check for pleural effusion or ascites, the presence of two kidneys, the size and shape of the kidneys and for any urinary tract obstruction.
- Consider complications:
  - Lipids - hyperlipidaemia.
  - Doppler ultrasound of leg veins in suspected deep vein thrombosis.
  - Abdominal ultrasound, renal vein Doppler scan, venography of the inferior vena cava, CT and MRI scanning of the abdomen if renal vein thrombosis is suspected.
  - Ventilation-perfusion scan - 'VQ' nuclear medicine lung scan; CT, pulmonary angiography for pulmonary embolism.
- Renal biopsy under ultrasound; renal biopsy may be helpful to guide diagnosis and treatment but is not indicated in all patients with nephrotic syndrome.

Management
Sodium and fluid restriction and high-dose diuretic treatment are indicated for most adults with nephrotic syndrome.

While most children with nephrotic syndrome respond to corticosteroids, 80% experience a relapsing course. Corticosteroids have reduced the mortality rate to around 3%. However, corticosteroids have well recognised potentially serious adverse effects such as obesity, poor growth, hypertension, diabetes mellitus, osteoporosis and behavioural disturbances.

Steroids have been used widely for the treatment of adult-onset minimal change disease but the response rates to immunosuppressive agents in adult minimal change disease, especially steroids, are more variable than in children. Intravenous albumin, prophylactic antibiotics and prophylactic anticoagulation are currently not recommended.

For children with idiopathic steroid-resistant nephrotic syndrome, studies have shown that calcineurin inhibitors (ciclosporin or tacrolimus) increase the likelihood of complete or partial remission compared with placebo/no treatment or cyclophosphamide.

About 80-90% of children with steroid-sensitive nephrotic syndrome (SSNS) have relapses. Eight-week courses of cyclophosphamide or chlorambucil and prolonged courses of ciclosporin and levamisole reduce the risk of relapse in children with relapsing SSNS compared with corticosteroids alone.

Vaccination: children with nephrotic syndrome should have the pneumococcal vaccination. Some children are also advised to have vaccination against chickenpox between relapses.

Referral and admission
Initial management should focus on investigating the cause, identifying complications and managing the symptoms of the disease.

Most patients do not require acute hospitalisation. All patients should be referred urgently to a nephrologist for further investigation. Indications for acute admission include:
• Severe generalised oedema, particularly if pleural effusion/oedema is causing respiratory compromise.
• Tense scrotal/labial oedema.
• Complications of the nephrotic state (e.g., sepsis, pneumonia, myocardial infarction, deep vein thrombosis).
• Inability to comply independently with therapy or with the condition in the family.
• Any features of a possible nephritic syndrome such as haematuria, hypertension and impaired renal function parameters.

Management principles

• Diet and fluids:
  • Reduce salt intake in the diet (avoid processed foods and adding salt to food).
  • Give a diet with adequate calorific intake and sufficient protein content (1-2 g/kg daily).
  • Fluid restriction is not usually necessary (if severe enough to need this then the patient may need admission).

• Hyperlipidaemia - does not initially require therapy but may do so if prolonged.

• Oedema:
  • Oedema is treated through diuretic therapy with furosemide (~1 mg/kg/day) ± spironolactone (~2 mg/kg/day).
  • Check weight regularly to assess response to diuretics and ensure fluid retention is not worsening, or that the patient is over-diuresed.
  • Patients with very low albumin levels may not respond to diuretics and may require admission to receive intravenous albumin therapy.
  • Some children with severe oedema may be prescribed antibiotic prophylaxis against infection and this should usually be on the advice of a renal specialist.

• Most children will have minimal change nephrotic syndrome and usually respond to a trial of steroid therapy under the direction of a renal specialist. Children in their first episode of nephrotic syndrome should be treated for two or three months with corticosteroids and there has not been found to be any advantage with a longer duration of treatment[9].
  • Other forms of nephrotic syndrome are less treatment-responsive; angiotensin-converting enzyme (ACE) inhibitors are frequently used in adults to some effect.
  • In children who do not respond to steroids, and in some adults, treatment may be with other immunomodulatory drugs such as cyclophosphamide, ciclosporin, tacrolimus and levamisole.
  • A number of new drugs, including rituximab, galactose and antifibrotic agents, are under investigation for the treatment of idiopathic focal and segmental glomerulosclerosis in adults[13].

Complications

Complications of nephrotic syndrome include:

• Decreased resistance to infections, due to urinary immunoglobulin loss.
• Increased risk of venous thromboembolism[14]. Adults with membranous nephropathy are at particular risk[15].
• Acute kidney injury may rarely occur as a spontaneous complication of nephrotic syndrome. Acute kidney injury may also be caused by excessive diuresis, interstitial nephritis due to use of diuretics or NSAIDs, sepsis or renal vein thrombosis[8].
• Chronic kidney disease may occur as a result of an underlying cause - eg, amyloidosis or diabetes[8].
• Steroid-resistant nephrotic syndrome is associated with a high risk of developing end-stage kidney disease[16].
• Increased risk of osteitis fibrosa cystica and osteomalacia due to loss of vitamin D-binding protein and its complexes in the urine, through a combination of calcium malabsorption and secondary hyperparathyroidism.

Prognosis

• This is very variable depending on the underlying cause.
• Congenital nephrotic syndrome usually carries a very poor prognosis.
• Corticosteroids have reduced the mortality rate in children to around 3%[17].
• Outlook for the vast majority of children with minimal change nephrotic syndrome is excellent, with good response to steroids, although there may be relapses and a need to use alternative immunomodulatory drugs.
• Since the introduction of corticosteroids, the overall mortality of primary nephrotic syndrome has decreased dramatically from over 50% to approximately 2-5%.
• The majority of children who present with their first episode of nephrotic syndrome achieve remission with corticosteroid therapy but over 70% experience a relapsing course[17].
• Adult prognosis is variable and largely related to the underlying cause, its severity, progression and response to any treatment used to modify it.
• For adults with idiopathic focal and segmental glomerulosclerosis, treatment may achieve complete or partial remission of proteinuria in 50-60% of patients and protect them from end-stage kidney disease but the remaining patients are resistant to currently available drugs[13].

Further reading & references


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