The nephrotic syndrome

Introduction

A clinical syndrome defined as proteinuria >3.5g/1.73m^2/day that is associated with hypoalbuminaemia, oedema, hyperlipidaemia, lipiduria (and thrombotic tendency).

The syndrome arises as a result of a failure of the glomerular filtration barrier to restrict the passage of proteins into Bowman's space. It implies structural abnormalities within the glomerular filter.

Primer: the glomerular filter (see 📖 p. 916)

- Comprises:
  - Charged endothelial cell glycocalyx layer.
  - Endothelium and its fenestrations.
  - The glomerular basement membrane (GBM).
  - Interdigitating podocytes that form a slit diaphragm.
- The passage of albumin, with its net negative charge, through the glomerular filter is prevented by size-specific factors (e.g. the slit diaphragm) and charge-specific factors (e.g. the anionic endothelial glycocalyx and GBM).
- Any albumin that escapes into Bowman's space is efficiently reabsorbed in the proximal tubule via receptor-mediated endocytosis. It is then degraded and returned to the circulation as peptide fragments.

Many primary and secondary causes of the nephrotic syndrome are now thought to be due to abnormalities of, or injury to, podocytes and the slit diaphragm ('podocytopathies').

How does proteinuria cause the clinical syndrome?

- The cause of hypoalbuminaemia is not as straightforward as one might think. The liver is actually capable of synthesizing 25g albumin/day: much higher than urinary losses.
- Potential explanations:
  - Larger quantities of albumin pass through the glomerular filter but are reabsorbed and catabolized within the renal tubules (i.e. the degree of proteinuria underestimates protein losses).
  - Other circulating factors alter the production of albumin by the liver in response to protein losses.
- Hypoalbuminaemia itself is not usually severe enough to directly explain the profound oedema of the nephrotic syndrome.
- Potential explanations:
  - The (classical) 'underfill' hypothesis: low plasma oncotic pressure →↓ circulating volume → Na^+ and water retention.
  - The 'overfill' hypothesis: proteinuria directly causes ↑ tubular Na^+ reabsorption.

- Hyperlipidaemia is caused by ↑ hepatic lipoprotein synthesis 2° to reduced plasma oncotic pressure.
- Thrombotic tendency is caused by ↑ hepatic synthesis of procoagulant factors, ↑ platelet aggregation, and ↑ urinary losses of anticoagulant factors.

Causes of the nephrotic syndrome

In descending order of frequency in adults:

- Membranous nephropathy.
- Minimal change nephropathy.
- SLE.
- Focal and segmental glomerulosclerosis.
- Mesangiocapillary (or membranoproliferative) glomerulonephritis (MCGN).
- Renal amyloidosis.
- IgAN.
- Light chain deposition disease.

► Diabetic nephropathy may also present with nephrotic range proteinuria and the nephrotic syndrome.

Investigation of the nephrotic syndrome

- SCr, eGFR, U&E, albumin and total protein, LFT, bone profile.
- Lipid profile (preferably fasting).
- Urine microscopy for casts or lipid bodies (📖 p. 25).
- uPCR (or uACR).
- Urinary selectivity index (particularly in children). Calculated as the transferrin:IgG ratio. Selective proteinuria refers to loss of proteins of lower MW (<100kDa), such as albumin or transferrin. Non-selective proteinuria includes proteins of higher MW, such as Igs (📖 p. 60).
- Consider full immunological and serological screen (📖 p. 40).
- USS kidneys.
- Renal biopsy (📖 p. 80).

The nephrotic syndrome: general management principles

Salt and fluid restriction

- ↑ Na^+ retention and ↑ blood volume → dependent oedema.
  - ▶ Monitor volume status carefully. Include regular measurement of weight, aiming for 0.5–1kg loss/day. Chart intake and output wherever possible (however, urinary tract catheterization is rarely necessary).
  - Salt-restrict to ≤2g/day.
  - Diuretics: a loop diuretic, such as furosemide, e.g. 40mg/day PO, increasing, as necessary, to 250mg daily. In massive oedema, IV diuretics may be required to overcome impaired oral drug absorption (2° to gut oedema).
  - Many clinicians use IV furosemide in combination with salt-poor albumin (e.g. 50–100mg furosemide in 100mL 20% human albumin solution over 1h) to augment natriuresis and diuresis; however, the enhanced effect may simply be due to volume expansion.
  - Add-on thiazide-type diuretics (e.g. metolazone 2.5–5mg PO od) may help to promote diuresis through a synergistic effect with high-dose loop diuretics (⚠ requires regular (often daily) measurement of Na^+ and K^+ to prevent profound electrolyte imbalances—use with caution, especially in an outpatient setting).

Reduction of proteinuria

- Proteinuria will itself aggravate tubulointerstitial inflammation (→ fibrosis) and ∴ accelerate renal damage and functional decline.
- Heavy proteinuria exposes nephrotic patients to infection and malnutrition.
  - Use ACE-I or ARB for their anti-proteinuric effect. Titrate carefully toward full dose (consider night-time administration if hypotension).
  - May reduce proteinuria by up to 50% at 8 weeks and ∴ prevent progression.
  - Treat ↑ BP, aiming for ≤125/75mmHg.
  - Protein restriction to 0.8g/kg/day. ⚠ This requires careful nutritional assessment and dietetic supervision.

Hypercoagulability

- Risk factors for thrombosis in nephrotic syndrome:
  - Duration of syndrome.
  - Degree of proteinuria.
  - Serum albumin <20g/L.
  - Underlying membranous nephropathy (📖 p. 564). ▶ Up to 20% of patients with nephrotic syndrome 2° to membranous nephropathy will develop a DVT.
- ▶▶ Breathlessness in a nephrotic patient may not always be 2° to volume overload; it may indicate pulmonary thromboembolism.

- Flank pain and haematuria suggest renal vein thrombosis (📖 p. 590).
- Prophylactic anticoagulation with SC heparin (and sometimes warfarin) in high-risk patients (📖 p. 892).
- Formally anticoagulate those with proven DVT or thromboembolic episode.
- Treat for the duration of the nephrotic syndrome; aim INR 2–3.

Infection

- Low IgG levels predispose to infection.
- Treat infections promptly, with appropriate cover for polysaccharide encapsulated organisms: *Strep pneumoniae, Neisseria meningitidis, Klebsiella pneumoniae, Haemophilus influenzae, Salmonella typhi, Cryptococcus neoformans, Pseudomonas aeruginosa* (mnemonic: **S**ome **N**asty **K**illers **H**ave **S**ome **C**apsule **P**rotection).
- Offer persistently nephrotic patients vaccination against pneumococcal disease.
- Infection may also complicate immune suppressive treatment of the nephrotic syndrome (📖 p. 540).

Dyslipidaemia

- Nephrotic syndrome →↑ hepatic synthesis and ↓ catabolism of LDL cholesterol (possibly in response to ↓ plasma oncotic pressure).
- Successful treatment of elevated LDL cholesterol may prevent CV morbidity and slow decline in renal function.
- Dietary restriction is usually insufficient and drug treatment with statins is often appropriate.
- Treatment of underlying nephrotic syndrome will lead to resolution of dyslipidaemia.