Nephrotic Syndrome

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General medicine,nephrology,ontheblogs,renal

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As a house officer and even as a registrar this is something I found difficult. Now as a renal registrar, I feel much more comfortable with it. However, I know I wasn't alone in finding it challenging, as this is something we often get phoned about. I'll go through it here but you can always find more on the Buku Medicine App, in the renal module (free on Apple and Android App stores).

What is nephrotic syndrome?

In a nutshell this is when the kidneys leak far too much protein. The filtering unit of the kidney is called the glomerulus. The glomerular basement membrane usually stops protein passing through. If the basement membrane is damaged (specifically the epithelial cells- the 'podocytes') the membrane becomes leaky and protein ends up in the urine.

It consists of the triad of:

1. Peripheral oedema
2. Low serum albumin (<30 g/L)
3. High urinary protein loss (urine PCR >300mg/mmol or urine ACR >250 mg/mmol)

How might it present?

Patients with nephrotic syndrome typically present with new onset peripheral oedema which can often be quite marked. They may also complain of shortness of breath (pleural effusions or pulmonary oedema), abdominal swelling (ascites), weight gain (from the fluid retention) or hypertension. They may also have noted foamy or frothy urine.

On examination they are often hypertensive and markedly fluid overloaded.

They often have a normal creatinine on their bloods. If measured their serum albumin will be low and their lipids will be high. A urine dipstick will have +++ protein.

If you're suspecting nephrotic syndrome the key investigations are:

1. Serum albumin <30g/L AND
2. Urinary protein:creatinine ratio (PCR) >300mg/mmol

Occasionally the cause of peripheral oedema is misdiagnosed as heart failure if the serum albumin is not dramatically reduced, so all patients with "?new heart failure" should have a urine dip and urine PCR if serum albumin is low.

Many hospitalised patients with a severe inflammatory response (for example due to sepsis) or decompensated liver cirrhosis will have low serum albumin and peripheral oedema, so getting the urinalysis and urine PCR is the key to diagnosis.

Note:

- **Urine PCR has replaced 24 hour urine collection as first line test to quantify proteinuria - it's quicker, easier to collect and accurate**
- **uPCR of >300mg/mmol is roughly equivalent to 3g of protein loss per day**
- **Equivalent urine albumin:creatinine ratio is roughly >200mg/mmol (urine ACR is an acceptable alternative test to uPCR)**

What next?

If a patient fulfils the diagnostic criteria above, or even just has lots of protein in their urine, discuss them with renal. I will go through what they might do next below.

In the meantime, there are a few extra diagnostic and management steps.

History

- **Do they have diabetes? If yes, for how long? How well is it controlled? Any complications e.g. retinopathy? Diabetes can cause nephrotic syndrome; if the patient has long standing diabetes and has had a gradual increase in proteinuria over years, then this typical history is sufficient to be confident their nephrotic syndrome is secondary to diabetic nephropathy.**
- **Do they have any other medical history?**
- **Have they started any new medications recently? Have they taken any NSAIDS recently?**
- **Any symptoms suggesting malignancy (weight loss, fatigue, bleeding, enlarged lymph nodes, bone pain)?**
- **Any symptoms suggesting rheumatological disease (arthritis, early morning stiffness, rashes)?**

Investigations

- **Full blood count, liver function tests, urea and electrolytes, calcium**
- **Coagulation profile and group and save (in case kidney biopsy required)**
- **Serum immunoglobulins, serum electrophoresis, serum free light chains (or urine for Bence Jones protein if this is used instead at your institution)**
- **Routine auto-antibodies, particularly ANA and double-stranded DNA**
- **Complement C3 and C4**
- **Hepatitis B & C, HIV**
- **Cholesterol – raised in nephrotic syndrome, additional support for diagnosis**
- **Blood sugar and HbA1c; steroid treatment risks causing hyperglycaemia**
- **Pregnancy test in females of child bearing age**
- **Renal tract US**
- **Renal may want an anti-PLA2R antibody; a specialist test that is specific for membranous nephropathy**

Management

- If they are fluid overloaded, start a loop diuretic (furosemide). Higher doses of loop diuretics are needed in hypoalbuminaemia. Nephrotic patients are highly salt avid so may require multiple diuretics to block different portions of the nephron, in order to achieve negative fluid balance and blood pressure control.
- Nephrotic syndrome is a big risk factor for venous thromboembolism (increases the risk at least 10x) - consider low molecular weight heparin.
- Treat hypertension. Diuretics are first line. Next line agents include ACE inhibitors (depending on renal function) and calcium channel blockers.
- Nephrology may want to do a biopsy so make sure they have a clotting sample and group and save sent.

Further nephrology workup

There are a number of conditions which can cause nephrotic syndrome. The renal team will try to figure out what the cause is through careful history and investigation. Ultimately, many people need a renal biopsy to help differentiate between the causes. In addition the causes can be primary or secondary - see table.

Disease on biopsy	Association
Diabetes	/
Amyloidosis	Primary amyloidosis or secondary to chronic inflammatory response e.g. rheumatoid arthritis, bronchiectasis
Minimal change disease	Hodgkin's lymphoma, NSAIDs, lithium
Membranous nephropathy	Malignancies, SLE and other autoimmune disorders, hepatitis B and C, NSAIDs, penicillamine, infection
Focal segmental glomerulosclerosis (FSGS)	Obesity, hypertension, sickle cell disease, HIV, hepatitis C, heroin, pamidronate
Membranoproliferative glomerulonephritis	Plasma cell dyscrasias, autoimmune disease, hepatitis B and C, essential cryoglobulinaemia

Causes of nephrotic syndrome

There are many causes of nephrotic syndrome. In some cases it is secondary to a systemic disease such as myeloma, amyloidosis and diabetes. Diabetes is the most common cause of the nephrotic syndrome. In general when diabetes is thought to be the most likely cause of the nephrotic syndrome, we do not perform a biopsy and the treatment is with an ACE inhibitor or Angiotensin receptor blocker.

It is important not to miss myeloma or amyloid as the cause of nephrotic syndrome. This may be diagnosed for the first time on a renal biopsy, however, the preliminary tests e.g. serum free light chains may already point to this diagnosis.

In nephrotic syndrome due to myeloma and amyloid the treatment is focused on treating the systemic disease e.g. chemotherapy for myeloma.

The most common primary causes are minimal change disease, membranous nephropathy and FSGS.

Minimal Change Disease

This is most commonly seen in children and young people but can present at any age. They classically present with sudden onset marked peripheral oedema.

Diagnosis: after the history and investigations above, renal biopsy is the investigation of choice. The biopsy is usually normal by light microscopy and immunofluorescence but electron microscopy reveals diffuse effacement of the podocyte foot processes.

Treatment is most commonly with high dose steroids. Minimal change typically has an excellent response to this. Tacrolimus and rituximab are alternatives, occasionally as first line but more typically for refractory disease or relapses. Minimal change disease typically responds excellently to treatment.

Membranous Nephropathy

More commonly affects older people. Hypertension is commonly seen. VTE is very common, even when compared to other causes of the nephrotic syndrome. In most cases it is caused by an antibody against the phospholipase A2 receptor - this can now be tested on a commercially available blood test.

Diagnosis is still usually confirmed with a biopsy, but if a biopsy is contraindicated making the diagnosis by the presence of anti PLA2R antibodies is acceptable.

Light microscopy usually shows thickening of the basement membrane. Occasionally ‘spikes’ in the basement membrane can be seen. Immunofluorescence will show granular capillary IgG±C3.

Electron microscopy shows subepithelial electron dense deposits and foot process effacement.

Mild membranous nephropathy is usually treated with ACE inhibitors and lifestyle advice alone. More severe membranous is treated with tacrolimus, rituximab or the ‘Ponticelli

regimen' - a combination of cyclophosphamide and prednisolone.

Focal Segmental Glomerulosclerosis (FSGS)

FSGS is a pattern that is commonly seen on renal biopsy - it can be idiopathic or can be secondary to another process affecting the kidney.

It is diagnosed on renal biopsy. Light microscopy shows a focal (affecting some, but not all glomeruli) and segmental (affecting part, but not all, of the glomerulus). Mesangial expansion, glomerular sclerosis and endocapillary hypercellularity are all often seen. Immunofluorescence does not show any immune deposits. Electron microscopy shows foot process effacement and podocyte degeneration.

Treatment is often started with high dose steroids, as in minimal change disease. Other options include tacrolimus and rituximab. FSGS typically responds less well to treatment than minimal change disease.

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