CASE 3

Short case number: 3.14.3
Category: Renal and Urinary Systems
Discipline: Medicine_nephrology
Setting: Urban: General Practice
Topic: Glomerulonephritis / nephrotic Syndrome

Case

50 year old Angela Durante, has been a patient of your practice for several years, she usually presents for pap smears and breast checks; and generally is well with no significant medical problems.

She presents today with a history of increasing ankle swelling and generally feeling tired and unwell. She comments that her urine has become quite cloudy. You note that her face seems swollen and that she looks more pale than usual.
Her urine analysis shows 3+ proteinuria.

Questions

1. Describe the pathophysiology of oedema due to following causes; low plasma oncotic pressure, increased capillary permeability and increased hydrostatic pressure.
2. What are the key features and history examination in Angela and why?
3. Define nephrotic syndrome.
4. Outline in a table how proteinuria is quantified and the clinical significance of this.
5. What is the underlying pathophysiology for the clinical features seen in nephrotic syndrome?
6. Angela has nephrotic syndrome – outline a plan of investigation including a rationale for the investigations undertaken.
7. What are the indications, contraindications and complications of renal biopsy?
8. What are the possible complications of nephrotic syndrome and how can these be prevented / managed?
9. Briefly outline the spectrum of glomerular diseases under the following headings, histology, immunology, pathogenesis, key clinical features and investigations.
10. Define acute renal failure and briefly describe the main causes and the clinical situations in which it can occur.

Suggested reading:

- Colledge NR, Walker BR, Ralston SH, Penman ID, editors. Davidson's Principles and Practice of Medicine. 22nd edition. Edinburgh: Churchill Livingstone; 2014. Chapter 17.

ANSWERS

1. Describe the pathophysiology of oedema due to following causes; low plasma oncotic pressure, increased capillary permeability and increased hydrostatic pressure.

Pathophysiology of oedema

A. Low plasma oncotic pressure

Low serum albumin due to

- increased loss - nephrotic syndrome
- decreased synthesis – liver failure
- malnutrition / malabsorption

B. Increased capillary permeability

Leakage of proteins into the interstitium, reducing the osmotic pressure gradient which draws fluid into the lymphatics and blood

- Local – infection / inflammation
- Systemic – severe sepsis
- Drug-related, e.g. calcium channel blockers

C. Increased hydrostatic pressure

High venous pressure / obstruction

- Deep venous thrombosis or venous insufficiency – local oedema
- Pregnancy
- Pelvic tumour
- Congestive heart failure
- Intravascular volume expansion (iatrogenic, renal failure, Conn's syndrome)

Lymphatic obstruction

- Infection – filariasis, lymphogranuloma venereum (Chlamydia trachomatis)
- Malignancy
- Radiation injury
- Congenital abnormality

2. What are the key features and history examination in Angela and why?

Signs of oedema - increasing ankle swelling, facial swelling – the latter excludes local factors e.g. venous thrombosis or insufficiency. The presence of cloudy urine and 3+ proteinuria on urine analysis focuses the problem to the kidneys. The symptoms of tiredness and feeling unwell and the appearance of apparent pallor are non-specific in determining the underlying cause. Enquire about a recent, apparent viral upper respiratory tract infection as a potential trigger for the current condition. The history "generally is well with no significant medical problems" makes the conditions that would be possible differential diagnoses e.g. congestive cardiac failure, cirrhosis, myxoedema, acute glomerulonephritis, less likely. Diabetes, as a potential cause, would have manifested with other symptoms.

3. Define nephrotic syndrome.

Nephrotic syndrome is not a disease, it refers to the secondary phenomena that occur when substantial amounts of protein are lost in the urine. The syndrome is characterized by heavy, overt proteinuria – usually > 3.5grms/ 24 hours (urine may be frothy), hypoalbuminaemia (<30g/l), oedema and generalized fluid retention, hyperlipidaemia and intravascular volume depletion with hypotension (or expansion with hypertension) may occur. Nephrotic syndrome is 15 times more common in children than adults. The diseases that cause nephrotic syndrome always affect the glomerulus.

4. Outline in a table how proteinuria is quantified and the clinical significance of this.

QUANTIFING PROTEINURIA		
24- HR urine protein	Protein/creatinine ratio[1] (random sample)	Significance
< 0.03g	<3.5 (female)[2] < 2.5 (male)[2]	Normal
0.03 – 0.3g	~ 3.5 – 15 [2,4]	Microalbuminuria
0.3 – 0.5g	~ 15 – 50[3]	Dipsticks positive
0.5 – 2.5g	~ 50 – 250[3]	Source equivocal
> 2.5g	>250[3]	Glomerular disease likely
> 4.0g	>400[3]	Nephrotic range – always glomerular

[1]Urine protein (mg/l) / urine creatinine (mmol/l)
[2]Usually measured as albumin/creatinine ratio
[3]Usually measured as total protein/creatinine ratio
[4]Not detectable with standard dipsticks but can be detected with specific 'albustix'

5. What is the underlying pathophysiology for the clinical features seen in nephrotic syndrome?

Filtration of low molecular weight anionic plasma proteins across the glomerular basement membrane is normally prevented by a negatively charged filtration barrier, which consists of proteoglycan molecules of heparan sulfate. In persons with nephrotic syndrome, the concentration of heparan sulphate mucopolysaccharide in the basement membrane is lower, and large amounts of protein cross the barrier and are excreted.

High glomerular permeability leads to hyperalbuminuria and, eventually, to hypoalbuminaemia. In turn, this lowers the plasma colloid osmotic pressure, causing greater transcapillary filtration of water and the development of oedema.

There is no evidence of decreased albumin synthesis in patients with nephrotic syndrome.

The structural changes believed to be responsible for causing proteinuria are (1) damage to the endothelial surface, causing loss of the negative charge,

(2) damage to the glomerular basement membrane (3) effacement of the foot processes (attached to the visceral surface of the glomerular basement membrane, the bases form the filtration slits). In the nephrotic state, levels of almost all lipids are elevated. Two pathogenic processes are operative, including (1) hypoproteinuria stimulating generalized protein synthesis in the liver, including the lipoproteins, and (2) diminution of lipid catabolism caused by reduced plasma levels of lipoprotein lipase.
Urinary immunoglobulin losses lower the patient's resistance to infections and increase the risk of serious sepsis and peritonitis. The loss of antithrombin III and plasminogen via urine and the simultaneous increase in clotting factors, especially factors I,VII,
VIII, and X, increases the risk for arterial thrombosis, venous thrombosis, and pulmonary embolism, which occurs in 5% of children with nephrotic syndrome.

6. Angela has nephrotic syndrome – outline a plan of investigation including a rationale for the investigations undertaken.

The following investigations aid in determining the aetiology and in planning and monitoring treatment.

- urinalysis, urine microscopy, testing for the ratio of urinary protein to urinary creatinine and a determination of light chain protein excretion (amyloid as primary cause)
- blood tests – serum creatinine, urea nitrogen, serum albumin and serum lipids. Full blood count, hepatitis B and C serology, antinuclear antibodies, serum complement levels,cryoglobulins, serum (or urine) protein electrophoresis.Antistreptolysin O titres, EBV IgM, IgG (depending on recent history).
  (to determine possible causes – postinfectious, collagen vascular disease e.g. SLE, leukaemia, lymphoma, hepatitis B, infectious mononucleosis etc)
- renal ultrasound to help establish the presence of 2 kidneys that are of normal size and architecture ie devoid of cysts and vascular malformations.
- renal biopsy to establish the nature and extent of renal disease in order to judge the prognosis and need for treatment.

7. What are the indications, contraindications and complications of renal biopsy?

Renal biopsy

INDICATIONS

- Acute renal failure that is not adequately explained
- Chronic renal failure with normal-sized kidneys
- Nephrotic syndrome or glomerular proteinuria in adults
- Nephrotic syndrome in children that has atypical features or is not responding to treatment.
- Isolated haematuria or proteinuria with renal characteristics or associated abnormalities

CONTRAINDICATIONS

- Disordered coagulation or thrombocytopaenia. Aspirin and

other agents causing platelet dysfunction should be omitted for elective biopsies.

- Uncontrolled hypertension
- Kidneys < 60% predicted size
- Solitary kidney (except transplants) (relative contraindication)

COMPLICATIONS

- Pain, usually mild
- Bleeding into urine, usually minor but may produce clot colic and obstruction
- Bleeding around the kidney, occasionally massive and requiring angiography with intervention, or surgery.
- Arteriovenous fistula, rarely significant clinically.

8. What are the possible complications of nephrotic syndrome and how can these be prevented / managed?

Consequences of the nephrotic syndrome and their management.

Feature	Mechanism	Consequence	Management
Hypoalbuminaemia	Urinary protein losses exceed synthetic capacity of the liver	Reduced oncotic pressure Oedema	Diuretics and a low sodium diet
Avid sodium retention	Low oncotic pressure and intravascular volume Secondary hyperaldosteronism ± Primary defect in renal sodium excretion	Oedema	(care to avoid over-diuresis)
Hyperlipidaemia	Non- specific increase in lipoprotein synthesis by liver in response to low oncotic pressure	High rate of atherosclerosis	Lipd-lowering drugs (e.g HMG CoA reductase inhibitors
Hypercoagulability	Relative loss of inhibitors of coagulation (e.g antithrombin III, protein C and S) and increase in liver synthesis of procoagulant factors	Venous thromboembolism	Case for routine anticoagulation in all patients with chronic or severe nephrotic syndrome
Infection	Hypogamma globulinaemia (urinary losses)	Pneumococcal infection	Consider vaccination esp. in children

9. Briefly outline the spectrum of glomerular diseases under the following headings, histology, immunology, pathogenesis, key clinical features and investigations.

17.41 GLOMERULONEPHRITIS: TYPES, ASSOCIATIONS AND CAUSES

	Histology	Immune deposits	Pathogenesis	Association	Clinical features
Minimal change	Normal, except on electron microscopy, where fusion of podocyte foot processes is seen (occurs in many types of proteinuria)	None	Unknown	Atopy, HLA-DR7 Drugs	Acute and often severe nephrotic syndrome Good response to corticosteroids Dominant cause of idiopathic nephrotic syndrome in childhood
Focal segmental glomerulosclerosis (FSGS)	Segmental scars in some glomeruli No acute inflammation Podocyte foot process fusion seen in primary FSGS with nephrotic syndrome	Non-specific trapping in focal scars	Unknown; in some, circulating factors increase glomerular permeability Injury to podocytes may be a common feature	Healing of previous localglomerular injury HIV infection, heroin misuse, morbid obesity	*Primary FSGS* presents as idiopathic nephrotic syndrome but is less responsive to treatment than minimal change; may progress to renal impairment, can recur after transplantation *Secondary FSGS* presents with variable proteinuria and outcome
Focal segmental (necrotising) glomerulonephritis	Segmental inflammation and/or necrosis in some glomeruli May be crescent formation	Variable according to cause, but typically negative (or 'pauci-immune')	Small-vessel vasculitis	Primary or secondary small-vessel vasculitis	Usually implies presence of systemic disease, and responds to treatment with corticosteroids and cytotoxic agents Check ANCA, ANA
Membranous nephropathy	Thickening of GBM Progressing to increased matrix deposition and glomerulosclerosis	Granular subepithelial IgG	Antibodies to a podocyte surface antigen, with complement-dependent podocyte injury (presumed from animal model)	HLA-DR3 (for idiopathic) Drugs Heavy metals Hepatitis B virus Malignancy	Usually idiopathic; common cause of adult idiopathic nephrotic syndrome One-third progress; may respond to chlorambucil/prednisolone Associated HLA class II allele varies in different populations
IgA nephropathy	Increased mesangial matrix and cells Focal segmental nephritis in acute disease	Mesangial IgA	Unknown	Usually idiopathic Liver disease	Very common disease with range of presentations, but usually including haematuria and hypertension (see text)
Mesangiocapillary glomerulonephritis (MCGN) (= membranoproliferative glomerulonephritis, MPGN)					
Type I	Mesangial cells interpose between endothelium and GBM	Subendothelial	Deposition of circulating immune complexes or	Bacterial infection Hepatitis B virus Cryoglobulin-	Usually proteinuria, may be haematuria Most common pattern found in association with subacute bacterial

	Histology	Immune deposits	Pathogenesis	Association	Clinical features
			'planted' antigens	aemia (± hepatitis C virus infection)	infection No proven treatments except where cause can be treated
Type II	Mesangial cells interpose between endothelium and GBM	Intramembranous dense deposits	Associated withcomplement consumption caused by autoantibodies	C3 nephritic factor and partial lipodystrophy	Also known as dense deposit disease
Post-infection	Diffuse (uniformly in all glomeruli) proliferation of endothelial and mesangial cells Infiltration by neutrophils and macrophages May be crescent formation	Subendothelial	Immune response to streptococcal infection Cross-reactive epitopes or other explanation	Streptococcal and other infections	Now rare in developed countries Presents with severe sodium and fluid retention, hypertension, haematuria, oliguria Usually resolves spontaneously
Goodpasture's disease (anti-GBM disease)	Usually crescentic nephritis	Linear IgG along GBM	Autoimmunity to α3 chain of type IV collagen	HLA-DR15 (previously known as DR2)	Associated with lung haemorrhage but either may occur alone Treat with corticosteroids, cyclophosphamide and plasma exchange to remove circulating autoantibodies
Lupus nephritis	Almost any histological type	Always positive and often profuse Pattern varies according to type	Some anti-DNA antibodies also bind to glomerular targets	Complement deficiencies Complement consumption	Very variable presentation, sometimes as renal disease alone without systemic features Responds to cytotoxic therapy in addition to prednisolone

10. Define acute renal failure and briefly describe the main causes and the clinical situations in which it can occur.

Acute renal failure (ARF) refers to a sudden and usually reversible loss of renal function, which develops over a period of days or weeks and is usually accompanied by a reduction in urine volume. There are many possible causes and it is frequently multifactorial

URINARY TRACT OBSTRUCTION

- Suggested by a history of loin pain, haematuria, renal colic or difficulty micturition but often clinically silent
- Can usually be excluded by renal ultrasound - essential in any patient with unexplained acute renal failure.
- Prompt relief of the obstruction restores renal function

VASCULAR EVENT

- Due to major vascular occlusion or small-vessel diseases , notably malignant hypertension and haemolytic uraemic syndrome/ thrombotic thrombocytopaenic purpura
- May be precipitated by ACE inhibitors in critical renal artery stenosis
- Urine usually shows minimal abnormalities but there may be haematuria in renal infarction.

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS (RPGN)

- Typically significant (dipsticks 3+) haematuria and proteinuria (often with red cell casts or 'glomerular' red cells)
- Sometimes associated with systemic features (e.g. systemic vasculitis, systemic lupus erythematosus (SLE), Goodpasture's (anti-GBM) disease)
- Useful blood tests include: antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies (ANA), anti-GBM antibodies, complement, immunoglobulins
- Renal biopsy shows aggressive glomerular inflammation, usually with crescent formation

ACUTE INTERSTITIAL NEPHRITIS

- Usually caused by an adverse drug reaction
- Characterized by small amounts of blood and protein in urine, often with leucocyturia
- Kidneys are normal size.
- Requires cessation of drug and often prednisolone treatment

DRUGS

For example:

- Haemodynamic effects (e.g NSAIDs, ACE inhibitors)
- Acute allergic interstitial nephritis
- Direct toxicity to the tubule (e.g. aminoglycosides – gentamycin, tobramycin)