Primary Cast Episode 29 - Renal & Endocrine Pathology

Host - Dr. Charlotte Durand
Guest - Dr. Jacqui Downey

These are smaller subjects so have been combined in this episode!

1. **Acute Kidney Injury** ***(note - in 2019 this exact question was asked using the term 'Acute Tubular Injury' - which was given as the reason for the patients drop in renal function in the clinical stem)***

   Acute Kidney injury is a clinico-pathological entity which involves an acute reduction in renal function and typically associated with tubular injury. It is usually reversible.

   What pathological processes can cause an AKI/Acute Tubular Injury? Please given an example of each.
   - Ischaemia due to decreased or interrupted blood flow. This can be associated with thrombosis (HUS, TTP, DIC), hypovolaemia, microangiopathies, malignant HTN or renal artery stenosis
   - Direct toxic injury to glomeruli/tubules - myoglobin, drugs, contrast injury, radiation
   - Acute Tubulointerstitial Nephritis - IgA nephropathy, infections, hypersensitivity to drugs, metabolic disease
   - Urinary obstructions by tumour, clot, stones, prostatic hypertrophy

   How does urine output change following Acute Kidney Injury?
   - This is highly variable but includes the following phases
   - Initiation phase: decreased urine output with elevation of urea (<36hours)
   - Maintenance phase: sustained decreased output (40-400mls/day), salt and water overload, uraemia, hyperkalaemia, metabolic acidosis
   - Recovery phase: increased output, hypokalaemia. Increased vulnerability to infection during this stage which may last for months.

2. **Urinary Tract Obstruction**
   What are the possible causes of urinary tract obstruction?
   Can divide these into Intrinsic (coming from within the tract) or extrinsic (i.e. outside the urinary tract)
   - Intrinsic
     - Congenital -urethral valves and strictures, bladder neck obstruction, ureteropelvic narrowing, reflux
     - Calculi
     - Internal tumours
     - Internal inflammation - urethritis, prostatitis
     - Blood clots
     - Sloughed papillae
   - Extrinsic

    - Tumours - prostate, bladder, cervix, uterus
    - Retroperitoneal fibrosis
    - Direct pressure - pregnancy, uterine prolapse, cystocoele
    - Prostatic hypertrophy
    - Functional - neurogenic bladder, dysfunctional ureter or bladder

What are the clinical features of obstruction

- Pain - due to distension or symptoms of underlying process i.e. renal colic, cystitis
- Polyuria and/or nocturia, hypertension and tubular acidosis in bilateral partial obstruction.
- Oligo/anuria, hyperkalaemia, raised urea/creatinine in complete bilateral obstruction.

What are the possible clinical sequelae of urinary tract obstruction?

- Infection
- Stone formation
- Atrophy/hydronephrosis/obstructive uropathy
- Renal failure and the complications of this

Describe the progression of effects of unrelieved obstruction of a ureter

- Reduced GFR
- Progressive dilation of the proximal ureter, renal pelvis and calyces (hydronephrosis)
- Renal parenchymal atrophy
- Blunting apices of the pyramids
- Interstitial inflammation leading to interstitial fibrosis
- Enlargement of the kidney
- Eventual result is a large, thin walled non-functional cystic structure

3. **Urolithiasis (Stones)**

What are the main types of renal calculi?

- Calcium oxalate and phosphate stones (70%)
- Struvite or triple stone (Magnesium, ammonium, phosphate) (15-20%)
- Uric acid stones (5-10%)
- Cysteine (1-2%)

What conditions favour stone formation?

- Increased concentration of stone constituents, changes in urinary pH, decreased urine volume, bacteria

What are the potential complications of ureteric calculi?

- Pain
- Haematuria

- Infection
- Obstructive renal impairment

4. **Post Strep Glomerulonephritis**

Describe the aetiology and pathogenesis of post strep glomerulonephritis

- Group A Beta-Haemolytic streptococci (90% are types 1, 4 or 12)
- Typically occurs after a pharyngeal or skin infection (impetigo)
- It is an immunologically mediated disease thought to be relating to immune complex deposition in the glomeruli
- Characterised by granular immune deposits in the glomeruli basement membrane leading to leakage of the glomeruli and acute proliferative glomerulonephritis
- The streptococcal antigen is found in the glomeruli of affected kidneys
- It causes complement activation - resulting in low serum complement
- There is also an elevated anti streptococcal antibody

Describe the clinical features of Post Strep GN in children

- Usually occurs 1-4 weeks after the strep initial infection
- Symptoms include malaise, fever, nausea, oliguria and haematuria (coke coloured urine)
- Red cell casts, proteinuria on urinalysis
- Periorbital and other oedema (less than nephrotic syndrome)
- Mild to moderate hypertension
- 95% of cases will recover in 1-3 weeks, 4% become chronic and 1% may progress into severe acute renal failure.

How does the clinical course differ in adults?

- Adult onset has a worse prognosis.
- 60% fully recover but it is a slow resolution. The others either develop chronic GN or rapidly progressive GN

5. **Nephrotic Syndrome**

What are the manifestations of nephrotic syndrome?

- Massive proteinuria
- Hypoalbuminaemia - with plasma albumin levels less than 30g/mL
- Generalised oedema
- Hyperlipidaemia and lipiduria

What are the mechanisms responsible for proteinuria?

Derangement of glomerular capillary walls resulting in increased permeability to plasma proteins. Structural damage and/or physiochemical alterations lead to massive proteinuria

What are the mechanisms underlying the hypoalbuminaemia?

- Mostly secondary to protein loss via the kidneys
- Inability of the liver to synthesise enough albumin to replace losses
- There is also increased catabolism of renally filtered albumin

What are the mechanisms underlying the oedema?

- Loss of colloid osmotic pressure
- Loss of serum albumin
- Accumulation of water and sodium in tissues
- Compensatory secretion of aldosterone (in response to hypovolaemia, increased ADH and increased sympathetic tone) worsens the oedema

What are the mechanisms underlying the Hyperlipidaemia and lipiduria

Hyperlipidaemia is due to abnormal lipid transport, increased liver synthesis and decreased catabolism. Lipiduria arises through a combination of increased glomerular filtration and the increased production.

What are the underlying causes of nephrotic syndrome?

- Primary glomerular disease
    - 95% of disease in kids - mostly minimal change disease, foc al segmental GN, membranoproliferative GN
    - 60% of disease in adults - focal segmental, membranous and a small amount is minimal change disease
- Systemic disease - mostly adults
    - Diabetes, amyloidosis, SLE, drugs (NSAIDs), infections (malaria, hepatitis), malignancies, others

6. **Pre-eclampsia (random - asked in 2008 so might not be asked but technically on the table)**

What is the pathogenesis and consequences of pre-eclampsia?

- Placental ischaemia is the key feature, leading to
- Reduction in PGI2 and PGE2
- Leads to increased renin/angiotensin II
- Combined with increased thromboxane A2 and endothelial dysfunction
- Results in systemic hypertension and DIC

Describe the clinical course of pre-eclampsia

- Usually seen after 32 weeks gestation, characterised by
- Hypertension, oedema and proteinuria
- Headache and visual disturbances are common
- Ecclampsia is characterised by seizures and coma

Describe the morphological changes that may be seen in the placenta in pre-ecclampsia

- Placental infarcts
- Retroplacental haematomas
- Villous ischaemia
  Note: (there are others but you just need 3 to pass so we picked these 3)

7. **Diabetes**

What are some of the principal complications of diabetes mellitus?

- Macrovascular changes - stroke, coronary artery disease, hypertension, peripheral vascular disease and atherosclerosis
- Microvascular - increased permeability of capillaries to plasma proteins, cerebral microangiopathy, nephropathy, retinopathy and peripheral neuropathy
- Pancreatic changes - loss of islet cells (in number and size), amyloid infiltration of islets
- Renal changes - sclerosis, thickening of the basement membrane, glomerulosclerosis
- Occular changes - haemorrhages, neovascularisation, detachment of the retina. Glaucoma.

Outline some of the differences between type 1 and type 2 diabetes (note - some of this is largely different in real life and there are a number more types of diabetes now recognised but we have kept the question in just in case as it's from 2014)

- Type 1
  - Onset in childhood, usually abrupt due to exhaustion of reserve
  - Patients often underweight
  - Decreased blood insulin
  - Circulating islet cell antibodies
  - Polyuria, polydipsia, polyphagia and ketoacidosis
  - Genetic link with T cell dysfunction that produced autoantibodies to islet cells
- Type 2
  - Often older at diagnosis
  - Less unwell at time of diagnosis
  - Often have a high BMI
  - No antibodies to islet cells
  - Less of a genetic component
  - Characterised by insulin resistance and high levels of insulin in the blood

8. **Type 1 Diabetes and DKA**

What is the typical pattern of onset of T1DM?

- Genetic predisposition
- Precipitating event i.e. intercurrent illness

- Autoimmune destruction if islet cells
- Subclinical then leading to overt DM

What environmental factors may contribute to the development of T1DM?
Infections - Group B coxsackie viruses, mumps, measles, CMV, rubella, EBV)
These may induce tissue damage and inflammation leading to release of B cell antigens, OR the viruses can produce antigens that mimic self antigens leading to the immune response cross reacting with self tissue

How does genetic susceptibility contribute to the development of T1DM?
There is a complex pattern of genetic associations which have been mapped to at least 20 loci.
Most important is the Class II MHC (HLA) locus which is responsible for 50% of total genetic susceptibility. Located on chromosome 6.
95% of white people with T1DM have one or more mutations at this location.
There are other non-MHC genes associated with insulin that can alter the protsin to make it less functional or less stable or may affect expression of insulin in the thymus, leading to altered selection of insulin reactive T-cells.

What is the pathogenesis of DKA?
Insulin deficiency and glucagon excess decreases the peripheral utilisation of glucose while increasing gluconeogenesis leading to severe hyperglycaemia
Hyperglycaemia causes osmotic diuresis and dehydration
Insulin deficiency increases lipolysis and free-fatty-acid production, which are converted to ketone bodies by the liver. If the rate of ketone bodies production exceeds rate of utilisation by peripheral tissues then it leads to ketonaemia and ketonuria
Decreased urinary excretion of ketones leads to systemic metabolic ketoacidosis

9. T2DM

What is the pathogenesis of T2DM?
Begins with insulin resistance, resulting in a decreased ability of the peripheral tissues to respond to secreted insulin . This occurs secondary to genetic predisposing factors and other metabolic factors.
There is both qualitative and quantitative beta cell dysfunction which manifests as inadequate insulin secretion in the face of insulin resistance and hyperglycaemia.
Initially, beta cell hyperplasia maintains normoglycaemia with higher levels of insulin secretion but then failure of this mechanism results in impaired glucose tolerance and then diabetes.

What is the genetic component with regards to T2DM?
Not HLA linked but there is a collection of multiple genetic defects that have been identified. The rates of T2DM in identical twins approached 80%,

What are the main adverse effects of severe sustained hyperglycaemia?
Osmotic diuresis - leads to hypovlaemia and increases risk of thrombosis
Electrolyte losses - Na, K, PO4
Hyperosmolarity - leading to changes in conscious state

10. Thyroid Stuff

Graves disease

What are the characteristic clinical findings in Grave's disease?

- Clinical hyperfunction of thyroid
- Thyroid gland enlargement
- Infiltrative ophthalmopathy
- Infiltrative dermopathy

What is the pathogenesis?

- Autoimmune mechanisms involving a variety of antibodies
- Auto-antibodies to TSH receptors
- IgG mimics of TSH which cause stimulation of the thyroid gland production

What is thyrotoxicosis?
Hypermetabolic state caused by elevated circulating levels of T3 and T4

What are the clinical features of thyrotoxicosis?

- Cardiac - tachycardia, dysrhythmias, cardiac failure
- Neuromuscular - tremor, proximal myopathy
- Ocular - wide staring gaze, lid lag, proptosis
- CNS - anxiety, emotional lability, insomnia
- Skin - warm, flushed, sweating
- Heat intolerance
- Thyroid storm - fever, tachycardia, arrhythmia, may be fatal unless treated promptly

11. Pituitary

How are pituitary adenomas classified?
Classification is based on hormone cell type

- Prolactin
- Growth hormone
- TSH
- ACTH
- Gonadotroph
- Can also be described as mixed, hormone positive or hormone negative.

What clinical syndromes may they produce?

- Prolactinoma: amenorrhoea, galactorrhoea, loss of libiao, infertility
- Somatotroph (GH): acromegaly

- ACTH: Cushing's Syndrome
- Gonadotroph: local effects from tumour i.e. headaches, visual impairment, diplopia, pituitary apoplexy plus hypogonadism - amenorrhoea, loss of libido and lethargy