Revise Nephrology Sydney
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Vasculitis and the Kidney

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Vasculitis- Inflamed vessel wall

- ***Presence of inflammatory leukocytes in vessel walls causing damage to the walls***
- Clinical manifestations due to:

  Vessel wall rupture- bleed

  Luminal compromise- downstream ischemia/necrosis
- Often serious and sometimes fatal; immunosuppressive therapy can cause poor quality of life
- Classified depending on the size of the blood vessel involved
- Kidneys often involved- especially those effecting small vessels
- **Skin,joint, muscle, peripheral nerve, GI tract, lung and kidney commonly involved**

Vasculitis Classification

- *Large vessel vasculitis*
  - Takayasu Arteritis
  - Giant Cell Arteritis
- *Medium sized vessels vasculitis*
  - Polyarteritis Nodosa
  - Kawasaki Disease
- *Small vessels vasculitis*
  - Pauci-immune : Granulomatosis with polyangiitis (Wegener's)
    - Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)
    - Microscopic polyangiitis
  - Immune complex mediated: Cryoglobulinemic vasculitis
    - IgA nephropathy/HSP
    - Anti-glomerular basement membrane (anti-GBM) disease

Vasculitis Presentation

- General symptoms: Fever and weight loss
- Skin: Purpura, livedo reticularis
- Muscles and joints: Myalgia or myositis, arthralgia or arthritis
- Nervous system: Mononeuritis multiplex, headache, stroke, visual loss
- Respiratory tract: Nose bleeds, bloody cough, lung infiltrates
- GI tract: Abdominal pain, bloody stool
- Kidneys: Glomerulonephritis, renal failure
- Heart and arteries: Myocardial infarction, hypertension

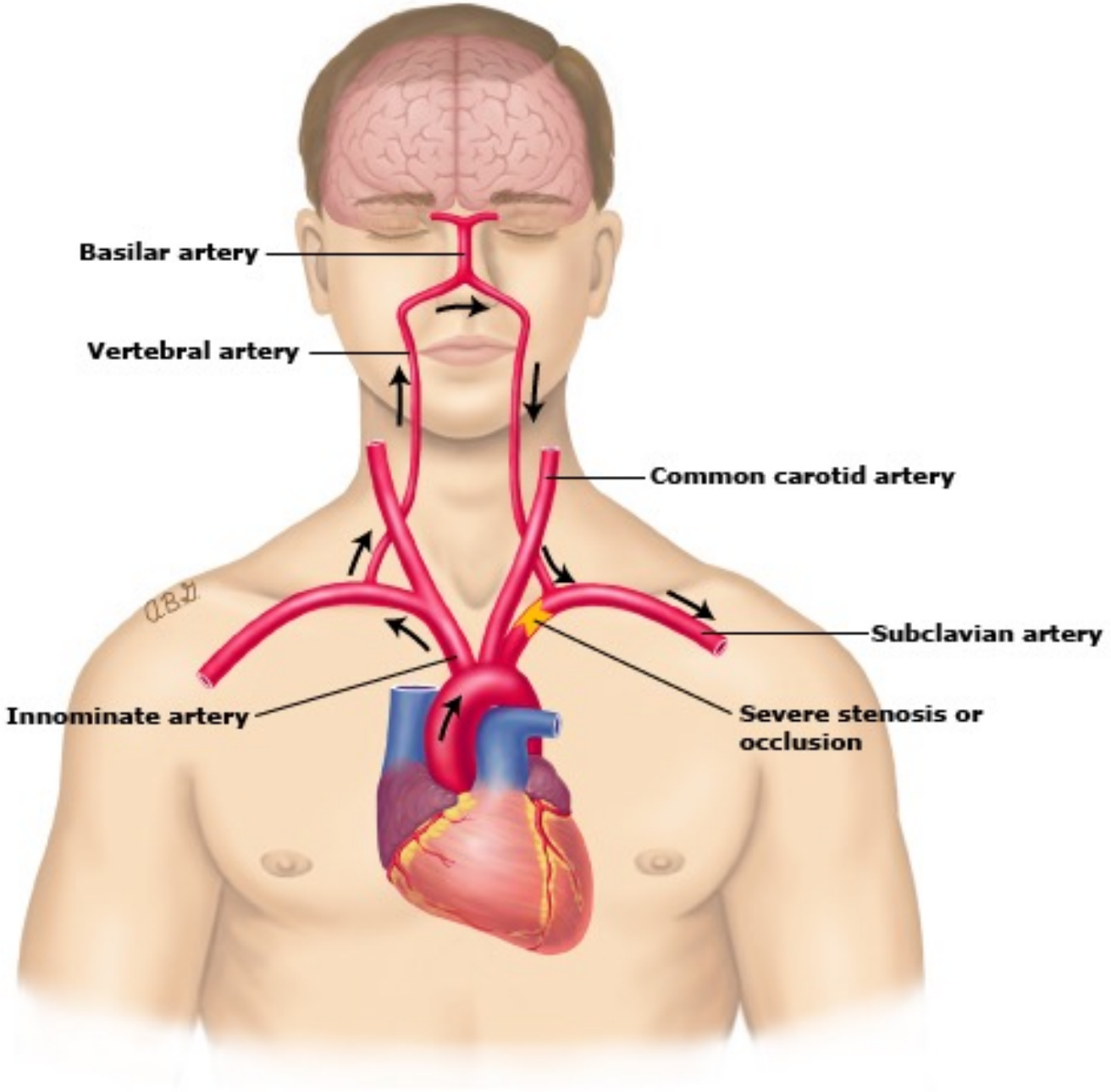
How is the kidney effected?

- Small vessel vasculitis- effect glomerular capillaries and thus lead to glomerulonephritis**……more exciting for the nephrologist…**
- Medium vessel vasculitis- Inflammation of interlobar/arcuate arteries causing thrombosis or rupture leading to renal infarction or haemorrhage respectively
- Large vessel vasculitis – effects aorta/main renal arteries leading to renovascular hypertension…..**almost like a renal artery stenosis….**

Takayasu Arteritis

- Women affected in 80 to 90% of cases and Asians more effected
- Age of onset usually between 10 to 40 years
- Primarily granulomatous inflammation of aorta and its branches- initially proximal subclavian artery then others
- Abdominal aorta effected eventually in 50%
- Aneurysmal dilatation or scarred stenosed vessel
- **Renal involvement:** Involvement of the renal arteries leads to renovascular hypertension in > 50% cases

Takayasu Arteritis picture



American College of Rheumatology criterion
Needs 3 out of 6

- Age at disease onset ≤40 years
- Claudication of the extremities
- Decreased pulsation of one or both brachial arteries
- Difference of at least 10 mmHg in systolic blood pressure between the arms
- Bruit over one or both subclavian arteries or the abdominal aorta
- Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities,

NOTE- Angina and aortic regurgitation may be seen

Fatigue, weight loss and low grade fever common

Takayasu Arteritis

- Angiography/CTA/MRA helpful
- Histologic confirmation often not possible
- Mainstay of treatment is glucocorticoids
- 50% need steroid sparing agents like methotrexate, azathioprine etc.
- Sometimes for irreversible stenosis- Percutaneous transluminal angioplasty or bypass grafts

Giant Cell Arteritis

As per American College of Rheumatology three positive out of following five criterion help to diagnose GCA:

- *Age greater than or equal to 50 years at time of disease onset*
- *Localized headache of new onset*
- *Tenderness or decreased pulse of the temporal artery*
- *Erythrocyte sedimentation rate (ESR) greater than 50 mm/hour*
- *Biopsy revealing a necrotizing arteritis with a predominance of mononuclear cells or a granulomatous process with multinucleated giant cells*

- <u>NOTE: Histologically Takayasu and GCA are similar</u>

Polyarteritis Nodosa (PAN)

- Systemic necrotizing transmural vasculitis that typically affects medium-sized muscular arteries
- ANCA negative/ lung characteristically NOT involved
- Involvement of smaller arteries(arterioles), veins and capillaries **excludes** PAN….so does GN exclude PAN?
- Aetiology unknown, 20-30% association with Hepatitis B
- Some association with Hepatitis C and Hairy cell leukemia
- Pathology- segmental transmural fibrinoid necrosis of arteries accompanied by leucocytes and leucocytoclasia…..and aneurysms….and no granulomas
- *Question- Granulomas characteristically associated with which vasculitis?*

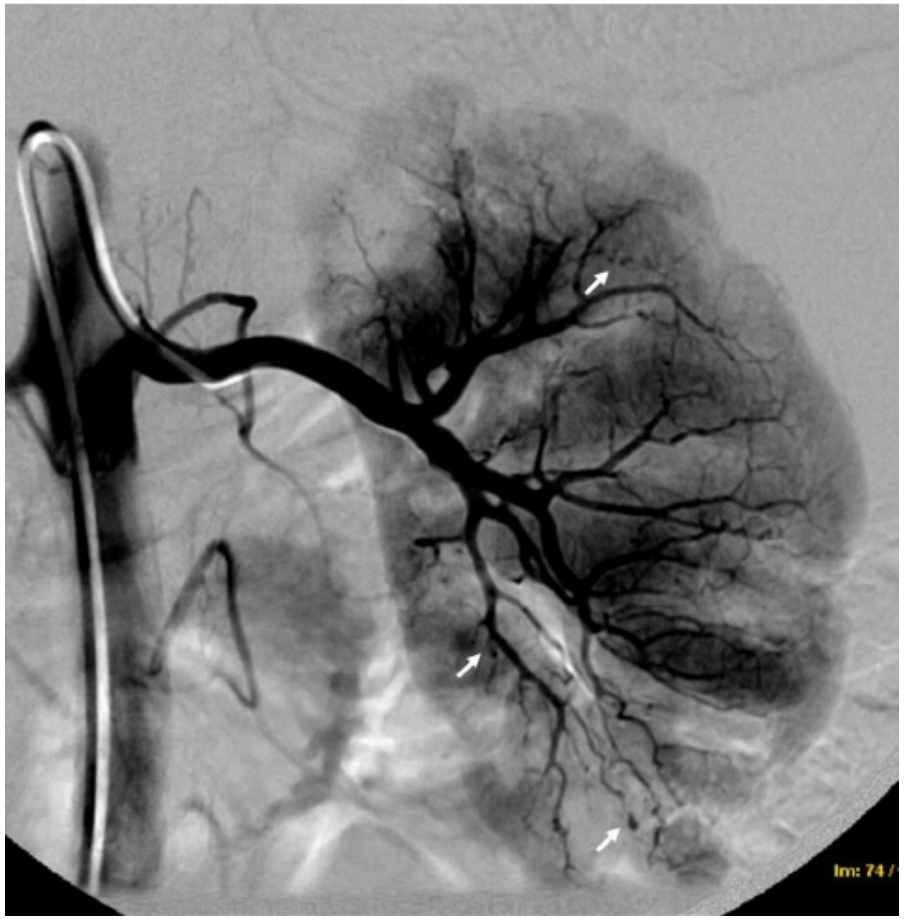
PAN presentation

• Systemic features- fever/malaise	• 80%
• Peripheral neuropathy	• 75%
• Arthralgia/myalgia	• 60%
• Skin- livedo reticularis,purpura	• 50%
• Kidney- AKI due to infarct/bleed	• 50%
• GI- abdominal pain, PR bleed	• 40%
• Hypertension	• 35%
• Orchitis	• 20%
• Stroke	• 20%
• Cardiomyopathy, pericarditis	• 10%

PAN diagnosis

- Biopsy of involved vessel where possible
- Mesenteric or renal arteriography often diagnostic- multiple aneurysms and irregular constrictions in medium sized vessels
- *REMEMBER- No GN, no lung involvement, no ANCA, no involvement of arterioles/capillaries/veins and no granuloma on biopsy*

PAN- Multiple aneurysms and constrictions



PAN Treatment

- Depends on disease severity and presence/absence of hepatitis B
- **Mild disease-** arthritis, anemia, and skin lesions but NO renal,cardiac,GI,neurologic involvement…treat with prednisolone
- **Moderate to severe disease-** involvement of above or life threatening complications…prednisolone and second immunosuppressive agent, typically cyclophosphamide initially followed by prednisolone and azathioprine for upto 18 months of total treatment
- **Hep B or C positive-** antiviral rather than immunosuppressive……..if severe PAN then short-term treatment with glucocorticoids and plasma exchange until antiviral therapy becomes effective….

ANCA Associated small vessel vasculitis

- Granulomatosis with polyangiitis (Wegener's):**90% ANCA +**[mostly PR3]
- Microscopic polyangiitis:**70% ANCA+** [mostly MPO]
- Eosinophilic granulomatosis with polyangiitis (Churg-Strauss): **50% ANCA+** [MPO slightly > PR3]
- **Beware-**

  -10-40% of Anti-GBM antibody disease ANCA+ [mostly MPO]

  - Drug associated ANCA vasculitis: most commonly anti-thyroid drugs, minocycline,hydralazine, cocaine contaminated with levamisole, penicillamine, clozapine and isoniazid

Q: What is ANCA??

Antineutrophil cytoplasmic antibody (ANCA)

- *Autoantibodies against antigens in the cytoplasm of neutrophils and monocytes*
- Two types of ANCA assays in wide use:

- Indirect immunofluorescence using alcohol-fixed buffy coat leukocytes (MORE SENSITIVE)

- Enzyme-linked immunosorbent (ELISA) using purified specific antigens (MORE SPECIFIC)

- Optimal approach: screen with immunofluorescence assays and if positive then confirm with ELISA

ANCA

- C-ANCA pattern: diffuse staining throughout cytoplasm with PR3 as the antigen most of the times
- P-ANCA: perinuclear pattern of staining (actually artefact of alcohol staining) with MPO as the usual antigen
- **Note**: False positive IF results for P-ANCA (e.g. in ulcerative colitis) could be due to other proteins e.g. lactoferrin, elastase, cathepsin G, bactericidal permeability inhibitor, catalase
- **Positive immunofluorescence ANCA always be confirmed with the quantitative ELISA**

Overview of pauciimmune vasculitis

- *Preceded by fever, malaise, anorexia, and weight loss for weeks to months*
- **Wegeners (GPA)**- granulomatous inflammation effecting upper and lower respiratory tracts with GN
- **Microscopic Polyangiitis-** Necrotising inflammation causing GN, pulmonary capillaritis but NO asthma/eosinophilia/granulomas
- **Churg-Strauss (EGPA)**- asthma, eosinophilia and necrotising granulomatous inflammation involving respiratory tract, renal involvement less common
- Prevalence is 2.5, 2.5 and 1/100000 respectively
- Renal biopsy **(COMMON IN ALL THREE PAUCI-IMMUNE VASCULITIS)** shows segmental necrotizing glomerulonephritis often with crescents, no granulomas/**IF negative**

Granulomatosis with polyangiitis (GPA)

- **Lung involvement in 90%-** pulmonary haemorrhage, nodular or cavitating lesions radiologically
- **ENT involvement in 90%-** sinusitis, rhinitis, subglottic stenosis, ocular inflammation, septal perforation and saddle nose deformity
- **Kidney involvement in 80%-** GN with/without proteinuria and renal failure, RPGN
- **Cutaneous manifestations** in 40%- leukocytoclastic angiitis causing purpura, ulceration and necrosis

Granulomatosis with polyangiitis (GPA)

- Less commonly- GIT, heart (pericarditis, myocarditis, conduction system abnormalities), neurologic system(asymmetric neuropathy, cranial nerve abnormalities, CNS mass lesion)
- **Diagnosis**- ANCA + in 90% (most commonly PR3/c-ANCA)

  - CXR and CT Chest

  - Renal biopsy (COMMON IN ALL THREE PAUCI-IMMUNE VASCULITIS) shows segmental necrotizing glomerulonephritis often with crescents, no granulomas/**IF negative (called pauciimmune GN)**

  - Nasal biopsy has high false negative rates, lung biopsy may help in occasional patient with no renal involvement

Microscopic Polyangiitis

- **Kidney involvement in 80%-** GN with/without proteinuria and renal failure, RPGN
- Lung involvement in 40% , GI in 40%, ENT in 35% and neurologic system in 30%
- MPO/p-ANCA + in more than 80%
- Renal biopsy same as Wegners…..but other site biopsy- NO GRANULOMA

Treatment of GPA and MPA

- IV methylprednisolone for three days followed by oral prednisolone at 1g/kg and Rituximab or Cyclophosphamide for induction(3-6 months)
- Remission in 85-90% in 3 months(75% achieve complete remission)
- Plasmapheresis offered to those needing dialysis or serum creatinine >350 micromol/L,RPGN on biopsy, haemoptysis or concurrent anti-GBM disease
- Maintenance therapy with azathioprine/rituximab and low dose prednisolone usually given for 12 to 24 months
- *REMEMBER: PJP prophylaxis with co-trimoxazole*
- RAVE and RITUXIVAS trial established non-inferiority of rituximab as induction therapy vs cyclophosphamide
- MAINRITSAN trial showed superiority of rituximab over azathioprine for maintainence therapy

‘Efficacy of remission-induction regimens for ANCA-associated vasculitis’

Specks U et al; N Engl J Med. 2013 Aug;369(5):417-27

PEXIVAS Trial (704 participants from 98 sites in 15 countries)

- Participants randomly assigned to 7 treatments of plasma exchange or no plasma exchange
- Standard-dose oral glucocorticoid regimen or a reduced-dose oral glucocorticoid regimen (<60% of the standard regimen by 6 months)
- Either cyclophosphamide (595-85% patients)or rituximab(109-15%)
- Followed for up to 7 years
- Conclusion -Plasma exchange did not reduce ESRD or death

-Lower rate of infections with low dose steroids with non-inferiority compared to standard dose in regards to endpoint

‘Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis’

Michael Walsh et al ; February 13, 2020
N Engl J Med 2020; 382:622-631
DOI: 10.1056/NEJMoa1803537

Eosinophilic Granulomatosis with polyangiitis (EGPA or Churg-Strauss Syndrome)

- Characterised by asthma and peripheral + tissue eosinophilia with vasculitis effecting multiple organs and extravascular granulomas
- Mean age of diagnosis 40 years (< 5% after age 65)
- Develops in sequential phases with overlap at times-

- *Prodromal phase* :In 2nd to 3rd decade with atopic disease/asthma

- *Eosinophilic phase*: pulmonary opacities, asthma, and peripheral eosinophilia with eosinophilic infiltration of lungs and GIT

- *Vasculitic phase*: In 3rd to 4th decade with vascular/extravascular granulomatosis and fever, weight loss, malaise, and lassitude

NO*TE: Asthma precedes vasculitis by up to 10 years and ENT involvement in up to 50%*

Diagnosis

- **As per Americal College of Rheumatology presence of four out of following six criterion is diagnostic-**
- Asthma
- Greater than 10 % eosinophils in blood
- Mononeuropathy (including multiplex) or polyneuropathy
- Migratory or transient pulmonary opacities detected radiographically
- Paranasal sinus abnormality
- Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas

Note- Kidney involvement in about 50% cases and less severe than GPA or MPA

Prognosis- Revised 2011 ‘Five Factors Score’ in EGPA

Cardiac involvement
Gastrointestinal disease (bleeding, perforation, infarction, or pancreatitis)
Renal insufficiency (plasma creatinine concentration >1.6 mg/dL [141 mmol/L])
Age>65 years
Absence of ENT manifestations (presence means better prognosis)

The FFS score ranges from 0 to 2: a score of 0 is given when none of the factors is present, a score of 1 for one factor, and score of 2 for two or more factors.

Treatment of Churg-Strauss Syndrome

- IV Methylprednisolone for 3 days followed by prednisolone 1 to 1.5mg/kg daily leads to remission in > 90%
- Cyclophosphamide added in cardiac/CNS involvement or FFS= or >2
- Once remission achieved (usually six months) switch to azathioprine or methotrexate with prednisolone weaning
- Azathioprine also used as steroid sparing agent in those needing>15 gm prednisolone
- Typical duration of therapy is 12-18 months
- SOME WITH MULTIPLE RELAPSES NEED INDEFINITE THERAPY

Trumpisms .....

- "There's nothing I love more than women, but they're really a lot different than portrayed. They are far worse than men, far more aggressive, and boy, can they be smart!”

- Trump held a joint news conference with the emir of Kuwait, Sheikh Sabah Ahmed al-Sabah, who complained about media coverage in his country. Trump said, "I'm very, very honoured and happy to know that you have problems with the media also.”

Thank you