Small Vessel Vasculitis

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Chapel Hill Consensus definitions of vasculitis 2012

- **Immune Complex Small Vessel Vasculitis**
  - Cryoglobulinemic Vasculitis
  - IgA Vasculitis (Henoch-Schönlein)
  - Hypocomplementemic Urticarial Vasculitis
    - (Anti-C1q Vasculitis)

- **Medium Vessel Vasculitis**
  - Polyarteritis Nodosa
  - Kawasaki Disease
  - Anti-GBM Disease

- **ANCA-Associated Small Vessel Vasculitis**
  - Microscopic Polyangiitis
  - Granulomatosis with Polyangiitis
    - (Wegener’s)
  - Eosinophilic Granulomatosis with Polyangiitis
    - (Churg-Strauss)

- **Large Vessel Vasculitis**
  - Takayasu Arteritis
  - Giant Cell Arteritis

Jennette et al Arthritis Rheum. 2013 Jan; 65(1):1-11
Overview

- HSP (IgA Vasculitis)
- ANCA associated vasculitides (AAV)
HSP
IgA Vasculitis
HSP classification criteria [Ozen S et al 2010, Ann Rheum Dis. 2010;69:798-806.]

Purpura, predominantly lower limb OR diffuse* (mandatory) PLUS 1 out of 4 of:

1. abdo pain
2. IgA on biopsy
3. haematuria/proteinuria
4. arthritis/arthritis

– *If diffuse (ie atypical distribution) then IgA deposition on biopsy required

Sn 100% Sp 87%
Epidemiology: UK

- Incidence is estimated at 20.4 per 100,000 children in the UK
  - Indian subcontinent: 24 per 100,000
  - White Caucasians: 17.8 per 100,000
  - Afro-Caribbean: 6.2 per 100,000
- Peak onset age 4 to 5 years of age, M>F
- Higher incidence during winter and the early spring
Pathogenesis
nature and nurture...
Infection

- ↑polymeric Gd-IgA1
- Anti glycan IgG or IgA1 bind Gd-IgA

Immune complexes
- IgA1-IgG, IgA1-IgA1, complement

Glomerular injury
Main clinical features

- Palpable purpura
- Arthritis or arthralgia
- Abdominal pain
- Gastrointestinal haemorrhage
- Glomerulonephritis
Other features

Intussusception
Pancreatitis
Pulmonary disease with haemorrhage
Orchitis
CNS involvement – fits and coma
Ureteric obstruction
Parotitis
Carditis
Guillain-Barre syndrome
Bullous HSP

Kausar S et al Journal of Dermatological Treatment. 2009; 20:88–90
HSP: Cerebral vasculitis

Bakkaloglu, S. A. et al. Nephrol. Dial. Transplant. 2000 15:246-248
Vascular deposition of IgA
HSP nephritis

- Focal and segmental proliferative glomerulonephritis
- 20-61% of HSP patients, depending on criteria for definition of nephritis
- Normally manifest between a few days and a few weeks after clinical presentation, but can occur up to 2 months or (rarely) more from presentation
Who needs a renal biopsy?

1. Nephritic/nephrotic presentation (urgent)
2. Raised creatinine, hypertension or oliguria (urgent)
3. Heavy proteinuria (Ua:Ucr persistently >100 mg/mmol) on an early morning urine sample at 4 weeks. Serum albumin not necessarily in the nephrotic range.
4. Persistent proteinuria (not declining) after 4 weeks?
HSP Treatment

• Supportive
• Steroids do not prevent nephritis
• For severe HSPN: lack of evidence base
  – Individualised: steroids, CYC, MMF, AZA, plasma exchange, others

Zaffanello M, Fanos V (2009) Treatment-based literature of Henoch-Schönlein purpura nephritis in childhood. Pediatr Nephrol. 24:1901–1911
HSPN: Rx based on severity

- **RPGN**: (>50% crescents) aggressive therapy with corticosteroid, cyclophosphamide and possibly plasma exchange
- **Severe nephritis** but not rapidly progressive (<50% crescents):
  - Corticosteroids alone or in combination with
  - CYC, AZA, MMF, others
- **Persistent proteinuria**: ACEI

Zaffanello M, Fanos V, 2009
Indication for steroid in non-renal HSP: personal practice

- Severe haemorrhagic oedema affecting the face or scrotum
- Severe bullous HSP
- Testicular involvement
- Severe gastrointestinal symptoms, particularly abdominal pain and gastrointestinal bleeding
- Other severe systemic manifestation:
  - pulmonary haemorrhage; cerebral vasculitis, pancreatitis etc
HSP outcome

• Benign

• But significant morbidity associated with cutaneous and gastrointestinal disease in short term and renal disease in the long term
Poorer renal prognosis

- Nephrotic syndrome
- Nephritic and nephrotic syndrome
  - 20% of patients with acute mixed nephritic and nephrotic syndrome progressed to end stage renal failure
  - 44 to 50% develop hypertension or chronic kidney disease
- Older children (>7 yrs) and adults
Duration of clinical features

- 1/3 of children have symptoms for less than 14 days
- 1/3 for 2-4 weeks
- 1/3 greater than 4 weeks
- Recurrence of symptoms occurs in around 1/3 of cases, generally within four months of resolution of the original symptoms.
  - Recurrences are more frequent in those with renal involvement.
Long term renal involvement in HSP

- Narchi et al 2005. ADC, 90:916-920
  - 1133 children (12 studies)
  - Renal involvement 34%
    - 80% isolated haematuria/proteinuria
    - 20% nephritis or nephrotic syndrome
  - Renal involvement occurred by 4 weeks in 85%
  - Persistent renal involvement in 1.8%
ANCA associated vasculitides

- Granulomatosis with polyangiitis (GPA) (formerly Wegener’s granulomatosis)
- Microscopic polyangiitis (MPA)
- Eosinophilic Granulomatosis with polyangiitis (EGPA; formerly Churg Strauss Syndrome)
ANCA

cANCA
PR3-ANCA

pANCA
MPO-ANCA
How do ANCA cause vasculitis?
How do ANCA cause vascular injury?
Why do patients develop ANCA? Nature and nurture...
• Type of ANCA more closely linked to genetics rather than clinical phenotype – Lyons et al; NEJM 2012

• PR3-ANCA: HLADP; SERPINA1; PRTN3

• MPO-ANCA: HLADQ
Granulomatosis with polyangiitis
(Wegener’s granulomatosis)
GPA (Wegener’s granulomatosis)
[2010, Ozen S et al ARD]

At least 3 out of 6 of the following criteria:

1. histopathology
2. upper airway involvement
3. laryngo-tracheo-bronchial stenoses
4. pulmonary involvement
5. ANCA positivity
6. renal involvement

Sn 93.3%  Sp 99.2%
Segmental left main bronchus stenosis
WG: lung
MPA
Microscopic polyangiitis

- Necrotizing SVV with few or no immune deposits
- Pulmonary capillaritis and glomerulonephritis (rapidly progressive renal failure)
  - But any organ can be affected
- pANCA; MPO-ANCA
- Renal Limited form (but watch out for other organ involvement)
Microscopic polyangiitis: alveolar haemorrhage
MPA: glomerulus
Microscopic polyangiitis (MPO-ANCA)

9A: Resected colon taken from a 13-year-old girl with microscopic polyangiitis (initially regarded clinically as renal limited vasculitis; MPO ANCA positive), and severe renal failure due to crescentic nephritis. Torrential gastrointestinal haemorrhage was the result of vasculitis affecting the colon, and a vasculitic ulcer is depicted.

9B: Magnetic resonance angiography (MRA) of the brain performed following acute visual loss in a 12 year old previously well female, with MPO ANCA positivity, but normal renal function. Multiple parieto-occipital haematomas are depicted. The intra and extra-cranial large and medium-sized arteries were normal, and the final diagnosis was MPO ANCA positive small vessel vasculitis of the brain.
Churg Strauss Syndrome
CSS

- Eosinophil rich and granulomatous inflammation, esp. of respiratory tract
- Necrotizing vasculitis of small and (possibly) medium vessels
- Associated with asthma and hypereosinophilia
- MPO-ANCA positivity
CSS in kids: n=32
Zwerina et al 2008

- All patients had significant eosinophilia and asthma
- Histological evidence of eosinophilia and/or vasculitis was present in virtually all patients
- ANCA were found in only 25%
ANCA to monitor disease activity and guide Rx?
Antiproteinase 3 Antineutrophil Cytoplasmic Antibodies and Disease Activity in Wegener Granulomatosis

Javier D. Finkielman, MD; Peter A. Merkel, MD, MPH; Darrell Schroeder, MS; Gary S. Hoffman, MD; Robert Spiera, MD; E. William St. Clair, MD; John C. Davis Jr., MD, MPH; W. Joseph McCune, MD; Andrea K. Lears, BS; Steven R. Ytterberg, MD; Amber M. Hummel; Margaret A. Viss; Tobias Peikert, MD; John H. Stone, MD, MPH; and Ulrich Specks, MD, for the WGET Research Group
Treatment
Standard treatment of AAV in children: “induction/maintenance”

- Induction:
  - Corticosteroids PLUS CYC (+/- PE) PLUS Antiplatelet agent
- Maintenance:
  - Low dose corticosteroid; AZA, MMF, other
- Rituximab: induction and/or maintenance
AAV outcome in children

- GPA: 40% develop renal failure; 12% mortality
- MPA: mortality 0-14%
- EGPA: mortality 18%
