Challenges in Diagnosis and Management of Vasculitis

Christian Pagnoux and Susa Benseler

Learning Objectives
The purpose of this workshop includes the following:
1. To review challenging clinical presentations of vasculitis in children and adults so that participants will be able to complete the following:
   a. Compare and contrast clinical presentations of vasculitis in children as compared to adults.
   b. Conduct an appropriate diagnosis work-up for vasculitis.
   c. Diagnose some more challenging vasculitides of children and/or adults.
Challenges in Diagnosis and Management of Vasculitis

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Learning Objectives
The purpose of this workshop includes the following:

2. To discuss evidence-based treatment approaches to vasculitis (case-based) so that participants will be able to complete the following:
   a. Evaluate the form and severity of vasculitis prior to deciding treatment.
   b. Establish an adequate therapeutic scheme for patients, integrating their individual characteristics, such as age.
   c. Understand the typical therapies used for vasculitis.
Challenges in Diagnosis and Management of Vasculitis

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Learning Objectives

The purpose of this workshop includes the following:

3. To review prognostic factors and long-term outcome of vasculitis across the age spectrum, enabling participants to:

   a. Identify prognostic factors of vasculitis and among those, which can be altered by treatment.
   b. Explain the different outcomes of vasculitis, according to patient and disease characteristics.
   c. Explain the need for long-term follow-up of children who achieved sustained remission.
   d. Organize and comment on the transition from paediatric to adult rheumatologists for the long-term follow-up of children with vasculitis.
Disclosure Statement

- **Susa Benseler**
  - Nothing to disclose

- **Christian Pagnoux**
  - *Consulting and speaker fees*: Hoffmann-La Roche, GSK
  - *Educational subventions (CanVasc)*: Hoffmann-La Roche, Euroimmun

Chapel Hill Nomenclature

EULAR/PRINTO/PRES classification

I Predominantly large vessel vasculitis
- Takayasu arteritis

II Predominantly medium sized vessel vasculitis
- Childhood polyarteritis nodosa
- Cutaneous polyarteritis
- Kawasaki disease

III Predominantly small vessels vasculitis
(A) GRANULOMATOUS
- Wegener’s granulomatosis
- Churg-Strauss syndrome
(B) NON-GRANULOMATOUS
- Microscopic polyangiitis
- Henoch-Schönlein purpura
- Isolated cutaneous leucocytoclastic vasculitis
- Hypocomplementemic urticarial vasculitis

IV Other vasculitides
- Behçet disease
- Vasculitis secondary to infection (including hepatitis B associated polyarteritis nodosa), malignancies, and drugs, including hypersensitivity vasculitis
- Vasculitis associated with connective tissue diseases
- Isolated vasculitis of the central nervous system
- Cogan syndrome
- Unclassified

Ozen et al.
Ann Rheum Dis.
2006;65(7):936-41
Patient: 5-year old girl (2009)

• March 13, 2009
  – Presentation to the ER at Sickkids with severe mid-abdominal pain, normal bowel movements, no blood in stool, no vomiting, low grade fever for 3 days
  – Bloodwork: raised ESR, CRP
  – Ultrasound: critical SMA stenosis
    ➢ Admission for workup
MRA

- Marked proximal stenosis and vessel wall thickening of the SMA and its branches with contrast enhancement
- Proximal stenosis of the left renal artery
Treatment March-Sept 2009

• 6 months “induction therapy”:
  – Cyclophosphamide IV monthly 750-1000mg/m²
  – High dose corticosteroids 2mg/kg, slow taper
  – Enoxaparin
MRA

- Improvement of the focal renal artery stenosis
- Stable appearance of enhancing vessel wall thickening of SMA and branches
Treatment October 2009-February 2010

- “maintenance therapy”:
  - Methotrexate 1 mg/m² /week
  - Moderate dose corticosteroids (25mg = 0.8mg/kg) slow taper
  - Enoxaparin
Treatment February-May 2010

• “Infliximab rescue therapy” 5mg/kg monthly IV in addition
• Methotrexate 1 mg/m2 /week
• Corticosteroids (10mg)
• Enoxaparin
Treatment May-August 2010

- Daily oral cyclophosphamide (50mg/day, 2mg/kg) plus high dose corticosteroids (60mg/day)
- Enoxaparin
Treatment August 2010-February 2011

- Daily oral cyclophosphamide (total 10 months) plus high dose corticosteroids (taper monthly)
- Enoxaparin
Inflammatory markers

C-R Protein

ESR
Inflammatory markers

C-R Protein

C-R Protein [mg/L]

mg/L


IV CYP HD PRED
MTX MD PRED
αTNF HD PRED
ORAL CYP HD PRED
AZA LD PRED
Inflammatory markers

IV CYP HD PRED
MTX MD PRED
αTNF HD PRED
ORAL CYP HD PRED
AZA LD PRED
Inflammatory markers

C-3 Complement

[Graph of C-3 Complement levels from Jan 2000 to Apr 2011]

PLT - blood

[Graph of PLT levels from Jan 2000 to Apr 2011]
Treatment March 2012

- Off Prednisone, on Imuran maintenance
- MRA stable, clinically claudication
- Exposure to 6 months of IV and 10 month of oral cyclophosphamide (cumulative dose: 17g)
- Moderate to high dose corticosteroids for 24 months (vertebral fractures, cataracts)
Large vessel vasculitis

Takayasu arteritis
Takayasu arteritis
PRES/EULAR 2005

Diagnosis TA: Angiography positive plus at least one criterion

Table 7  Classification criteria for Takayasu arteritis

Angiographic abnormalities (conventional, CT, or MR) of the aorta or its main branches (mandatory criterion), plus at least one of the following four features:
• Decreased peripheral artery pulse(s) and/or claudication of extremities
• Blood pressure difference >10 mm Hg
• Bruits over aorta and/or its major branches
• Hypertension (related to childhood normative data)

CT, computed tomography; MR, magnetic resonance.
TA Histology

- Inflammatory infiltrate and concentric thickening of intima, media and adventitia
- Mononuclear infiltrate: T cells, macrophages
Treatment of TA in children
Treatment of TA in adults
EULAR recommendations for the management of large vessel vasculitis

C Mukhtyar,1 L Guillemin,2 M C Cid,3 B Dasgupta,4 K de Groot,5 W Gross,6 T Hauser,7 B Hellmich,8 D Jayne,9 C G M Kallenberg,10 P A Merkel,11 H Raspe,6 C Salvarani,12 D G L Scott,13 C Stegeman,10 R Watts,14 K Westman,15 J Witter,16 H Yazici,17 R Luqmani,1 for the European Vasculitis Study Group

Ann Rheum Dis 2009;68:318-3
Table 5  The seven recommendations for the management of large vessel vasculitis with the level of evidence for each statement and the median strength of recommendation as per EULAR operating procedures

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Treatment of refractory TA
Rationale:
anti-TNF in Takayasu Arteritis

• TNFα → granuloma formation

• Increased serum TNFα in patients with Takayasu

• Higher TNFα production from CD3+ T cells in patients with active disease

Park. Rheumatology. 2006;45:545-8
Anti-tumour necrosis factor therapy in patients with refractory Takayasu arteritis: long-term follow-up

E S Molloy, C A Langford, T M Clark, C E Gota, G S Hoffman

- Retrospective single-centre study of 25 patients with refractory Takayasu Arteritis
  - Stable remission could not be achieved with use of low-dose prednisone (<10mg/day)

- Outcomes:
  - Partial or complete remission
  - Disease relapse
  - Adverse events associated with anti-TNF therapy

Remission

• Complete and sustained remission:
  – Absence of features of active disease
  – Absence of new lesions on imaging studies
  – No glucocorticoid therapy for at least 6 months

• Partial remission:
  – Glucocorticoid dose reduced by at least 50%
Table 1  Immunosuppressive therapies (other than prednisone) taken prior to the initiation of anti-tumour necrosis factor (TNF) therapy by the 25 patients with Takayasu arteritis (TAK)

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<tr>
<th>Agent</th>
<th>No. (%)</th>
<th>Duration of therapy* in months, median (range)</th>
<th>Maximum dose, median (range)</th>
</tr>
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<tr>
<td>Methotrexate</td>
<td>22 (88)</td>
<td>9 (1–144)</td>
<td>20 mg/week (15–27.5)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>10 (40)</td>
<td>6 (1–12)</td>
<td>150 mg/day (50–150)†</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>5 (20)</td>
<td>16 (1–48)</td>
<td>150 mg/day</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>3 (12)</td>
<td>4 (1–4)</td>
<td>2 g/day (2–3)</td>
</tr>
<tr>
<td>Ciclosporine A</td>
<td>2 (8)</td>
<td>3</td>
<td>100 mg twice a day</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>2 (8)</td>
<td>4</td>
<td>6 mg/day</td>
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Where no range is provided, all patients received the agent in question at the same dose and/or for the same duration.

*Duration of therapy prior to the initiation of anti-TNF therapy. †One patient received monthly intravenous cyclophosphamide.
Patients

• 22/25 were female (88%)

• Mean age 35 years (range 15-64)

• Mean age of disease onset 25 years (range 10-53)
Outcome Etanercept

Figure 1  Outcome of treatment of refractory patients with Takayasu arteritis (TAK) with etanercept (ETA). IFX, infliximab.
**Outcome Infliximab**

**Figure 2** Outcome of treatment of refractory patients with Takayasu arteritis (TAK) with infliximab (IFX).
Prednisone therapy

• Discontinued in 60%
  – After a median interval of 10 months (range 0-72)
  – Prednisone-free remission maintained for a median duration of 30 months (range 6-82)

• Tapered <10mg/day in 28%
Relapses during anti-TNF therapy

- Four patients with major disease relapse
  - New stenotic lesions
  - Elevated inflammatory markers
  - Three patients achieved remission on higher doses of anti-TNF therapy
Adverse events

• Abnormal liver function tests

• Primary histoplasmosis (after 2 infusions)

• Breast cancer (after 41 months of therapy)
Christian, 32 years-old

- No family history
- Minor asthma (salbutamol puffs, PRN)
- Married, 4 healthy children
- Smoker (5 packs-year)

- 2009: R temporal artery prominence, then R temporal headaches and fatigue
Christian, 32 years-old

- BP 120/80 symmetrical, normal auscultation
- All pulses +, with prominent R>L temporal arteries and behind ears, not tender

- Normal ESR and CBC
- Doppler-US: enlarged R TA 1.1 x 0.6 cm, versus L 0.25
Christian, 32 years-old

• **Diagnosis?**
  1. « Temporal Takayasu? »
  2. « GCA/LVV of the youth? »
  3. Other systemic vasculitis with TA involvement?
  4. TA fibromuscular dysplasia?
  5. Ehlers-Danlos (type IV)?
  6. Other?

• **Biopsy?**

• **Treatment?**
ACR criteria as the silver standard...

1. Age $\geq 50$ years,
2. New-onset localized headache,
3. Temporal artery tenderness or decreased temporal artery pulse,
4. ESR of at least 50 mm/h,
5. Abnormal artery biopsy specimen characterized by mononuclear infiltration or granulomatous inflammation, giant cells

3/5 criteria $\rightarrow$ sensitivity 93.5%, specificity 91.2%

1990 Criteria for the Classification of Takayasu Arteritis

1. Age at disease onset < 40 years
2. Claudication of extremities
3. Decreased brachial artery pulse
4. BP difference > 10 mm Hg
5. Bruit over subclavian arteries or aorta
6. Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities

≥3 criteria → sensitivity 90.5%, specificity 97.8%

Ehlers-Danlos Syndrome Type IV

- Hereditary, DA, with \textit{COL3A1} mutation (50\% de novo)
- **Major diagnostic criteria:**
  - Arterial rupture
    - Intestinal rupture
    - Uterine rupture during pregnancy
    - Family history of EDS type IV
- **Minor diagnostic criteria:**
  - Thin, translucent skin (especially noticeable on the chest/abdomen)
  - Characteristic facial appearance (thin lips and philtrum, small chin, thin nose, large eyes)
  - Acrogeria
  - Arteriovenous carotid-cavernous sinus fistula
  - Hypermobility of small joints
  - Tendon/muscle rupture
  - Early-onset varicose veins
  - Pneumothorax/pneumohemothorax
  - Easy bruising Chronic joint subluxations/dislocations
  - Congenital dislocation of the hips
  - Talipes equinovarus (clubfoot)
  - Gingival recession
Christian, 32 years-old

• 2010-2011: L temporal artery increased in size, with some occasional tenderness
Christian, 32 years-old

- 2010-2011: L temporal artery increased in size, with some occasional tenderness

- Left TABx:
  - mixed infiltration with eosinophils, lymphocytes and rare plasma cells
  - disruption of elastic layers
  - intimal proliferation and fibrosis
  - organizing thrombus filling the lumen with recanalization
  - no giant cells, granuloma or necrosis

*Ito et al. 2008*
Juvenile temporal arteritis (JTA)

• 1975, Lie et al. (JAMA)
• « Nodules » in the TA region of children or young adults
• Bx: occlusion of lumen by intimal proliferation as well as intra- and peri-vascular eosinophil infiltration (no giant cell)
• Main differential diagnoses:
  – Kimura disease
  – Angiolymphoid hyperplasia with eosinophilia
  – Thromboangiitis obliterans with eosinophilia

Nesher et al. Semin Arthritis Rheum 39
Juvenile temporal arteritis (JTA)

- Diagnostic criteria
  - Children or young adults (7-44 years)
  - Absence of associated features (myalgias, visual disturbance, fever, anemia)
  - Manifested as painless temporal nodule
  - Normal ESR (mild eosinophilia)
  - Eosinophilic panarteritis and thrombosis with or without microaneurysmal disruption of the artery
  - Intimal proliferation, disruption of the media and extensive infiltrate consisting of lymphocytes, eosinophils and plasma cells
  - Absence of granulomatous infiltration and giant cells

Vasculitis of the TA in the Young

- Systemic vasculitis with TA involvement
- Juvenile temporal arteritis
  - And its differential diagnoses/overlaps (Kimura)
- “Elderly-Type” TA in the young
  - rare (17 to 45 years old)
  - GCA in young or “noneosinophilic JTA (with giant cells)”?
- Overall, the latter two carry good prognosis
  → No treatment?

Nesher et al. Semin Arthritis Rheum 39
Izeult, 32 years-old

- Married, no children
- No significant medical history
- Sinusitis since 1994 (14 years-old)
- 1996: saddle-nose deformity
  
  nasal/sinus biopsy: vasculitis
  cANCA antiPR3+
Izeult, 32 years-old

- Sinusitis since 1994 (14 years old)
- 1996: saddle-nose deformity
  nasal/sinus biopsy: vasculitis
  cANCA antiPR3+

→ Methotrexate + Prednisone
Izeult, 32 years-old

• Do you agree with this therapeutic choice?
  1. YES
  2. NO
  3. I am OK with this choice, but I would have treated her with a different drug/agent
  4. I have no idea
EARLY SYSTEMIC GPA (<150 µM)

NORAM

- Methotrexate vs oral Cyclophosphamide for induction
- Non-inferiority trial (d=15%) for remission at 6 months
- 100 p. with “early systemic” GPA for 12 months

Remission at 6 mo
MTX 89.8%
CYC 93.5% (P=0.04)

Relapse at 18 mo
MTX 69.5%
CYC 46.5% (P=0.02)

CYC Leukopenia
MTX liver enzymes

CS at M18
8.8 g MTX vs 6.2 CYC
(P<0.01)

Izeult, 32 years-old

• Methotrexate + Prednisone until 2004

• 2005: sinusitis, recurrent lacrimal duct obstruction then voice hoarseness & **stridor**...
Bronchial stenoses in GPA

- 7 GPA patients with endobronchial stenoses (1991-2004 in 4 French centers – 5F/2M)
- Cough and dyspnea (all), minor hemoptysis (4), some “stridor” (4) ... lung collapse

Bronchial stenoses in GPA

- 7 GPA patients with endobronchial stenoses (1991-2004 in 4 French centers – 5F/2M)
- Cough and dyspnea (all), minor hemoptysis (4), some “stridor” (4)
- With SGS or low tracheal involvement in 3

SGS in GPA

Elective location, 1-2 cm below the vocal cords (junction of 2 embryological segments?)*

3-23%, F>M, ~35 y-old
3% FVSG 500 p. F58%
9.3% VCRC 268 p. F68%
16% NIH 1992 158 p.
23% Cleveland 1996, 43% isolated at Dx, aged 26, F 63%

14% ARChiVe (n=65)
25% Denver (n=28)
50% Cleveland (n=28)!!!

Fowler et al. (Cleveland) ACR 2012, Chicago #1531

Bronchial stenoses in GPA

• 7 GPA patients with endobronchial stenoses (1991-2004 in 4 French centers – 5F/2M)
• Cough and dyspnea (all), minor hemoptysis (4), some “stridor” (4)
• With SGS or low tracheal involvement in 3
• Not isolated at Dx, but isolated during 2 relapses
• Bx: inflammation (7), granuloma (5), vasculitis (2)

Izeult, 32 years-old

• Local treatment?
  1. Yes
  2. No
  3. I don’t know

• Systemic treatment?
  1. Prednisone + cyclophosphamide
  2. Prednisone + methotrexate
  3. Prednisone alone
  4. Prednisone + rituximab
  5. Can not decide...
Subglottic stenosis
Local treatment

• Dilations (balloons or bougies)
• Corticosteroid injections

• Topical mitomycine (in vitro antifibroblastic)

• Laser deobstruction → secondary stenosis
• Diathermy deobstruction
• Stents
• Surgery (reconstructive procedures, permanent tube-free speech-ready tracheostomy)

Systemic treatment

Corticosteroids....

+ ???
CYCLOPS

- **Open label RCT**
- **149 AASV (40% GPA)**
- **No Iº hypothesis**
- **Pulse (IV or oral) vs continuous oral CYC**
  - **Remission at 9 mo**
    - Pulse 88.1%
    - Continuous 87.7%
  - **IV pulse = lower rate of leukopenia**, HR 0.41
    - [CI, 0.23 to 0.71]
- **At 18 mo:**
  - 14.5% relapsed
  - (18.8% IV vs. 9.4% PO)

RELAPSES

- 15 (20.8%) DO
- 30 (39.5%) pulse had ≥1 relapse
- Total of 21 relapses (10 renal) in the DO vs. 54 (12 renal) in the pulse limb
- Cox regression analysis
  \[ HR=0.50, \text{ 95\% (CI, 0.26-0.93); } p=0.029 \]

Rituximab in SGS

• Aries et al, Ann Rheum Dis 2006;65:853–858 (1/month x 4)
  – 1/2 patients “improved significantly”, but not before month 4

  – 11 patients with SGS
  – “Vasculitis affecting the sub-glottis […] responded to treatment without recurrence, but left permanent damage”
Rituximab in SGS

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>Response</th>
<th>Complete Remission</th>
<th>Improved</th>
<th>Stable Disease</th>
<th>Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbital mass (n=27)</td>
<td>27</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Meningitis (n=12)</td>
<td>12</td>
<td></td>
<td></td>
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<tr>
<td>Subglottic stenosis (n=8)</td>
<td>8</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Pulmonary masses (n=12)</td>
<td>12</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Alveolar hemorrhage (n=12)</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glomerulonephritis (n=26)</td>
<td>26</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis (n=6)</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyneuropathy/Mononeur. (n=4)</td>
<td>4</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Figure 3** Efficacy of rituximab (RTX) by organ involvement given for the most frequent organ involvements (in at least four patients or more). For efficacy of RTX in organ involvements that were less common see online supplementary material.

Ontario public drug program

EXCEPTIONAL ACCESS PROGRAM REIMBURSEMENT CRITERIA

Effective February 29, 2012, RITUXAN is approved for the induction of remission of severely active Granulomatosis with Polyangiitis (GPA) OR microscopic polyangiitis (MPA) as combination treatment with glucocorticoids, in patients who meet all of the following criteria:

1. The patient must have severe active disease that is life- or organ-threatening. At least one supporting laboratory and/or imaging report must be provided. The organ(s) and how the organ(s) is(are) threatened must be specified.

2. There is a positive serum assays for either proteinase 3-ANCA (anti-neutrophil cytoplasmic autoantibodies) or myeloperoxidase-ANCA. A copy of the laboratory report must be provided.

3. Cyclophosphamide cannot be used for the patient for at least ONE of the following reasons:
   a) The patient has failed a minimum of six IV pulses of cyclophosphamide; OR
   b) The patient has failed three months of oral cyclophosphamide therapy; OR
   c) The patient has a severe intolerance or an allergy to cyclophosphamide; OR
   d) Cyclophosphamide is contraindicated; OR
   e) The patient has received a cumulative lifetime dose of at least 25 g of cyclophosphamide; OR
   f) The patient wishes to preserve ovarian/testicular function for fertility.

The initial treatment would be a once weekly infusion dosed at 375 mg/m$^2$ x 4 weeks.
Patient: 5 year old girl

• HPI:
  – Presented to Sickkids ER with headache, behavior change, vomiting, low grade fever
  – Cluster of seizures in ER, admission to ICU in seizure status
Patient: 5 year old girl

- **pmHx:**
  - Healthy
  - No exposures
Examination

• **O/E**
  
  – Vital signs: tachycardia, Temp 38.0°C, normal blood pressure, unwell
  
  – General physical examination: normal

  – **Neurological examination:**
    
    • hyperreflexic, photophobic
    
    • severe headaches
    
    • Seizure status, continues bilateral seizures
Laboratory tests

- ↑ ESR 48 mm/h, ↑ CRP 32mg/dl, ↑ WBC 28, normal diff
- CSF: 31 WBC, 90% lymph, (↑) protein
- ↑ Opening pressure 38 cm H2O (N<20)
- Infectious, rheumatologic, metabolic w/u negative
MRI

- White and grey matter lesions,
- Leptomeningeal contrast enhancement
MRA, Conventional Angiography

normal
Clinical suspicion of inflammatory brain disease or childhood CNS vasculitis
Newly acquired focal and/or diffuse neurological deficits, and/or psychiatric symptoms including regression in a previously healthy child

Initial evaluation
- Blood inflammatory markers:
  CRP, ESR, vWF, CBC/differential, C3 complement, albumin, IgG, coagulation, workup for systemic diseases
- MRI arthrogram:
  Inflammatory lesions in the parenchyma (T2, FLAIR, gadolinium enhancement), ischemic lesions (DWI, ADC), meningeal contrast enhancement and vessel-wall imaging (mural gadolinium enhancement)

Targeted evaluation for inflammatory brain disease or childhood PACNS
- Blood markers
  Neuronal antibodies, anti-NMO antibody, oligoclonal banding, genetic testing
- CSF analysis
  Opening pressure, cell count, protein, encephalitis registry, neuronal antibodies, oligoclonal banding
- Conventional angiography

Suspicion of angiography-negative childhood CNS vasculitis or other CNS disease requiring tissue confirmation
- Brain biopsy
  Lesional (MRI) or nonlesional (nondominant hemisphere, frontoparietal lobe); full thickness including leptomeninges, gray and white matter

Nonvasculitic inflammatory brain disease
- Mimic of inflammatory brain disease or CNS vasculitis
- Other diagnosis

Confirmed diagnosis of angiography-positive childhood CNS vasculitis

Small vessel cPACNS mimics

Autoimmune/autoinflammatory diseases
- Celiac disease
- Familial hemophagocytic lymphohistiocytosis
- Hashimoto's encephalitis
- Sarcoidosis
- Systemic lupus erythematosus

Demyelinating disorders
- Acute demyelinating encephalomyelitis
- Multiple sclerosis

Neuronal antibody-associated inflammatory brain diseases
- NMDA-receptor associated encephalitis
- Neuromyelitis optica
- Limbic encephalitis

T-cell mediated inflammatory brain diseases
- Rasmussen encephalitis

Infectious or post-infectious
- Influenza virus
- JC virus (progressive multifocal leukoencephalopathy)
- Mycoplasma pneumoniae
- Streptococcus pneumoniae

Metabolic
- Leukodystrophies
- Mitochondrial diseases
- Mucopolysaccharidoses

Neoplastic
- Lymphoma

Nutritional
- Vitamin B12 deficiency
Small vessel cPACNS mimics

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Metabolic
- Leukodystrophies
- Mitochondrial diseases
- Mucopolysaccharidoses

Neoplastic
- Lymphoma

Nutritional
- Vitamin B12 deficiency

Cellucci 2010, Current Opinion Rheumatology
Demyelinating diseases

- Inflammation targets white matter and causes demyelinating plaques
  - Myelin filled macrophages

- Parenchymal inflammatory disease:
  - CD68+ macrophages on brain biopsy

Courtesy Cynthia Hawkins, July 2011
Neuronal antibody associated IBrainD

- Direct antibody binding
- Targets: cell surface receptors, channels, enzymes
- No complement in brain parenchyma

Dalmau 2005
Anti-NMDAR Encephalitis

Dalmau et al. Lancet Neurology 2010

N=400
Antibodies cross-link and cause internalization of NMDAR

Hughes. J Neuroscience 2010 + Courtesy of M. Batthish
### NMDA Receptor Encephalitis

<table>
<thead>
<tr>
<th>Symptom Presentation</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women and girls</td>
<td>91</td>
</tr>
<tr>
<td>Median age, range (years)</td>
<td>22, 5-76</td>
</tr>
<tr>
<td>Prodromal symptoms (information available for 84 patients)</td>
<td>72</td>
</tr>
<tr>
<td><strong>Psychiatric (first seen by psychiatrist)</strong></td>
<td>77</td>
</tr>
<tr>
<td><strong>Neuropsychiatric (first seen by neurologists)</strong></td>
<td>23</td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td></td>
</tr>
<tr>
<td>Any type</td>
<td>76</td>
</tr>
<tr>
<td>Generalised tonic-clonic</td>
<td>45</td>
</tr>
<tr>
<td>Partial complex</td>
<td>10</td>
</tr>
<tr>
<td>Other*</td>
<td>30</td>
</tr>
<tr>
<td><strong>Dyskinesias and movement disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Any type</td>
<td>86</td>
</tr>
<tr>
<td>Orofacial</td>
<td>55</td>
</tr>
<tr>
<td>Choreaathetoid and complex movements with extremities, abdomen or pelvis</td>
<td>47</td>
</tr>
<tr>
<td>Abnormal postures (dystonic extension), muscle rigidity, or increased tone</td>
<td>47</td>
</tr>
<tr>
<td>Other†</td>
<td>25</td>
</tr>
<tr>
<td>Autonomic instability‡</td>
<td>69</td>
</tr>
<tr>
<td>Central hypoventilation</td>
<td>66</td>
</tr>
</tbody>
</table>

Dalmau, 2008
Neuromyelitis optica NMO

- Auto-antibodies against Aquaporin4
- CSF ± serum

Figure 1
Aquaporin 4 is a type III water channel regulator with limited surface exposed residues. AQP4 has been
NMO

Banwell, 2008
Limbic encephalitis

- **Paraneoplastic** antibodies
  - Hu, Ma
- Auto-antibodies against LGI
  - Secreted antigen associated with **Voltage-gated potassium channels**
    - AMP: anchor protein for LGI
    - AMP-binding protein

Dalmau 2005, 2010
Haberlandt, Bien 2010
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Newly acquired focal and/or diffuse neurological deficits, and/or psychiatric symptoms including regression in a previously healthy child

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- Other diagnosis

Confirmed diagnosis of angiography-positive childhood CNS vasculitis

Brain biopsy

Lymphocytic small vessel vasculitis
Diagnosis:
Primary CNS Vasculitis of childhood
Angiography-negative, small vessel SVcPACNS
Modified Calabrese criteria: cPACNS

- Clinical evidence of a newly acquired focal and/or diffuse neurological deficit or psychiatric syndrome in a patient ≤18 years of age plus
- angiography and/or brain biopsy evidence of CNS vasculitis
- in the absence of a significant underlying condition known to cause or mimic CNS vasculitis

Calabrese, 1988
Benseler 2005, 2006
Primary CNS Vasculitis of Childhood

Angiography-positive cPACNS
Large vessel disease

Angiography-negative cPACNS
Small vessel disease

Benseler 2005, 2005
Elbers, 2011
Brain blood vessels

MCA
ACA
ICA
PCA
Basilar artery

Small vessels: Angiography negative
SVcPACNS protocol
# SVcPACNS treatment protocol

## Anticoagulation
- Heparin/LMWH x 2 weeks
- Aspirin 3-5mg/kg/d

## Immunosuppression
- **Induction therapy x 6 months**
  - IV cyclophosphamid pulse
    - (500-750mg/m\(^2\) monthly x 7)
  - Prednisone 2mg/kg/d x 1 month
    - (monthly taper: 60-50-40-30-25-20-17.5-15-12.5-10-7.5-5-2.5mg)
- **Maintenance therapy x 18 month**
  - MMF 800-1200mg/m\(^2\)/d
  - (Azathioprine 2mg/kg/d max 150mg)

---

Hutchinson, 2010 *Lancet Neurology*
SVcPACNS treatment protocol

- Diagnosis
- 6 Months
- 12 Months
- 18 Months
- 24 Months

**PSOM**
- E'parameter
- MRT/MRA/CA
- Biopsy
- PedsQL
- PGA

** PGA**

**PGA**

**MRT**
- PedsQL
- CAT-B
- PGA

**Cyclophosphamid**

**Prednisone**

**Mycofenolate (Azathioprine)**

- Prednisone
- Mycofenolate (Azathioprine)
at 24 months

- 69% had **NO** functional neurological deficit

*Figure 3: Neurological outcome in children with small vessel childhood primary angiitis of the CNS, as measured by the paediatric stroke outcome measure score*

Hutchinson, 2010 Lancet Neurology
SVcPACNS Flares

Diagnosis  
6 Months  
12 Months  
18 Months  
24 Months

Azathioprine

Relapse: ON

Cyclophosphamide

Prednisone

MMF
Conclusions

• Similarities and differences between children and adult vasculitides

• Collaboration is needed and beneficial

• Long-term follow-up of patients is essential
  – Relapsing diseases
  – Long-term damage and delayed complications
  → Transition clinics
Get on board!