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.**

CANADIAN RHEUMATOLOGY ASSOCIATION | SOCIÉTÉ CANADIENNE DE RHUMATOLOGIE

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.**

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Challenges in Diagnosis and Management of Vasculitis

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Learning Objectives

The purpose of this workshop includes the following:

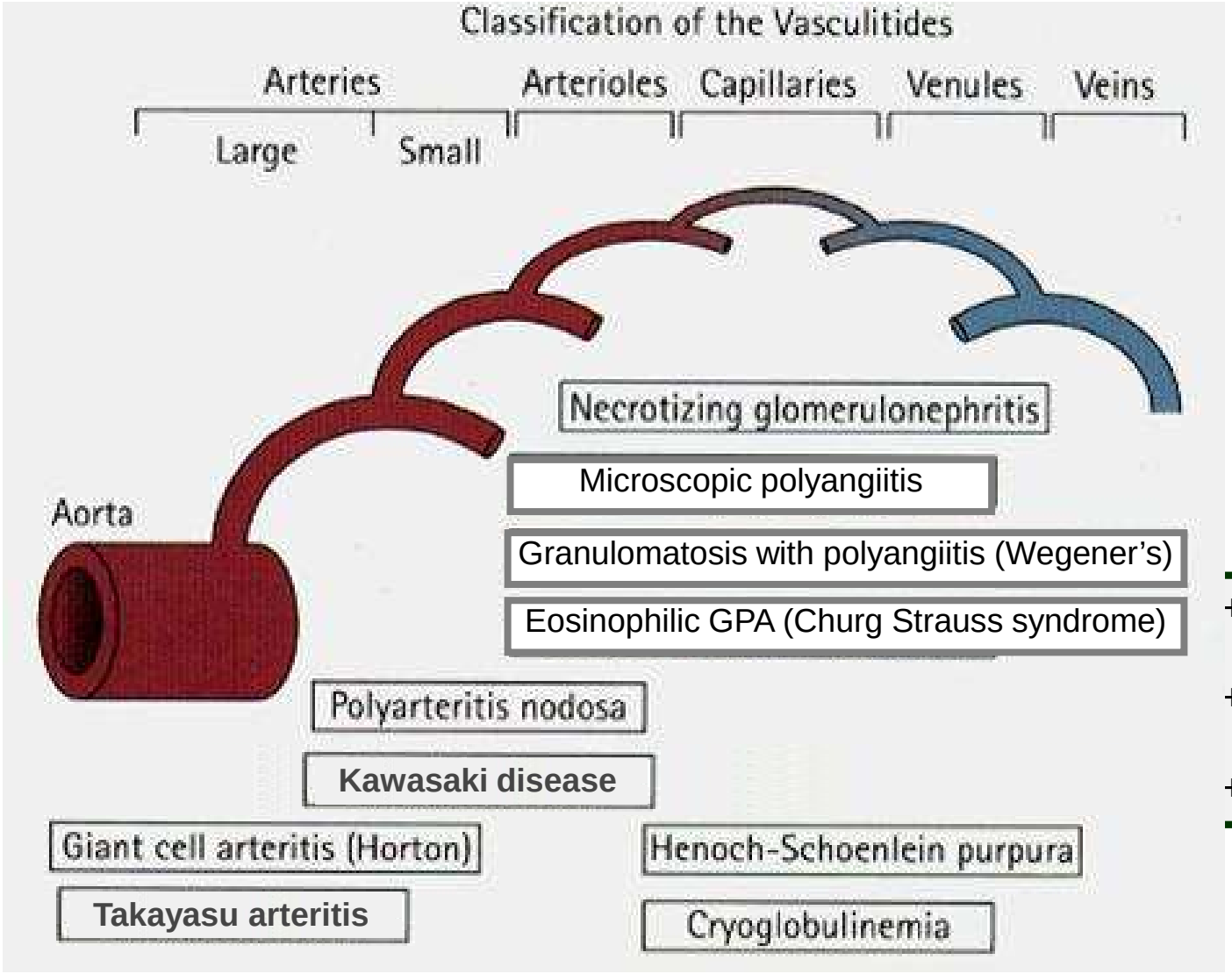
3. **To review prognostic factors and long-term outcome of vasculitis across the age spectrum, enabling participants to:**
    a. **Identify prognostic factors of vasculitis and among those, which can be altered by treatment.**
    b. **Explain the different outcomes of vasculitis, according to patient 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.**

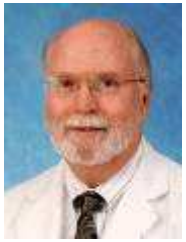
Disclosure Statement

- 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





+ antiGBM

+ Behçet

+ CNS-V

Jennette et al. Arthritis Rheum 1994;37:187-92
Falk et al. Arthritis Rheum 2011 Apr;63(4):863-4

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

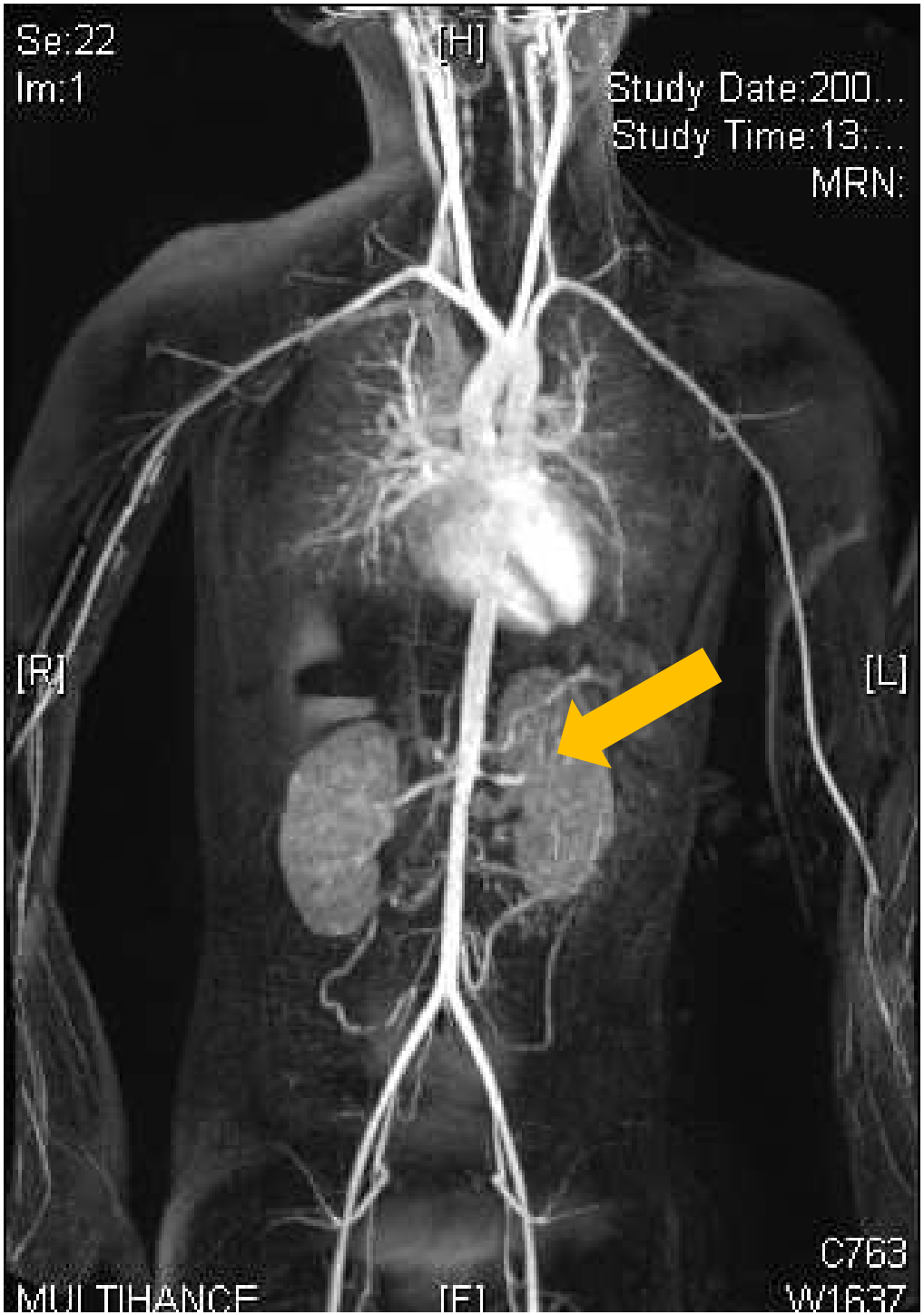
(B) NON-GRANULOMATOUS
- Microscopic polyangiitis
- Henoch-Schönlein purpura
- Isolated cutaneous leucocytoclastic vasculitis
- Hypocomplementic urticarial vasculitis

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 vomitting, low grade fever for 3 days
  - Bloodwork: raised ESR, CRP
  - Ultrasound: critical SMA stenosis
  - ➢ Admission for workup

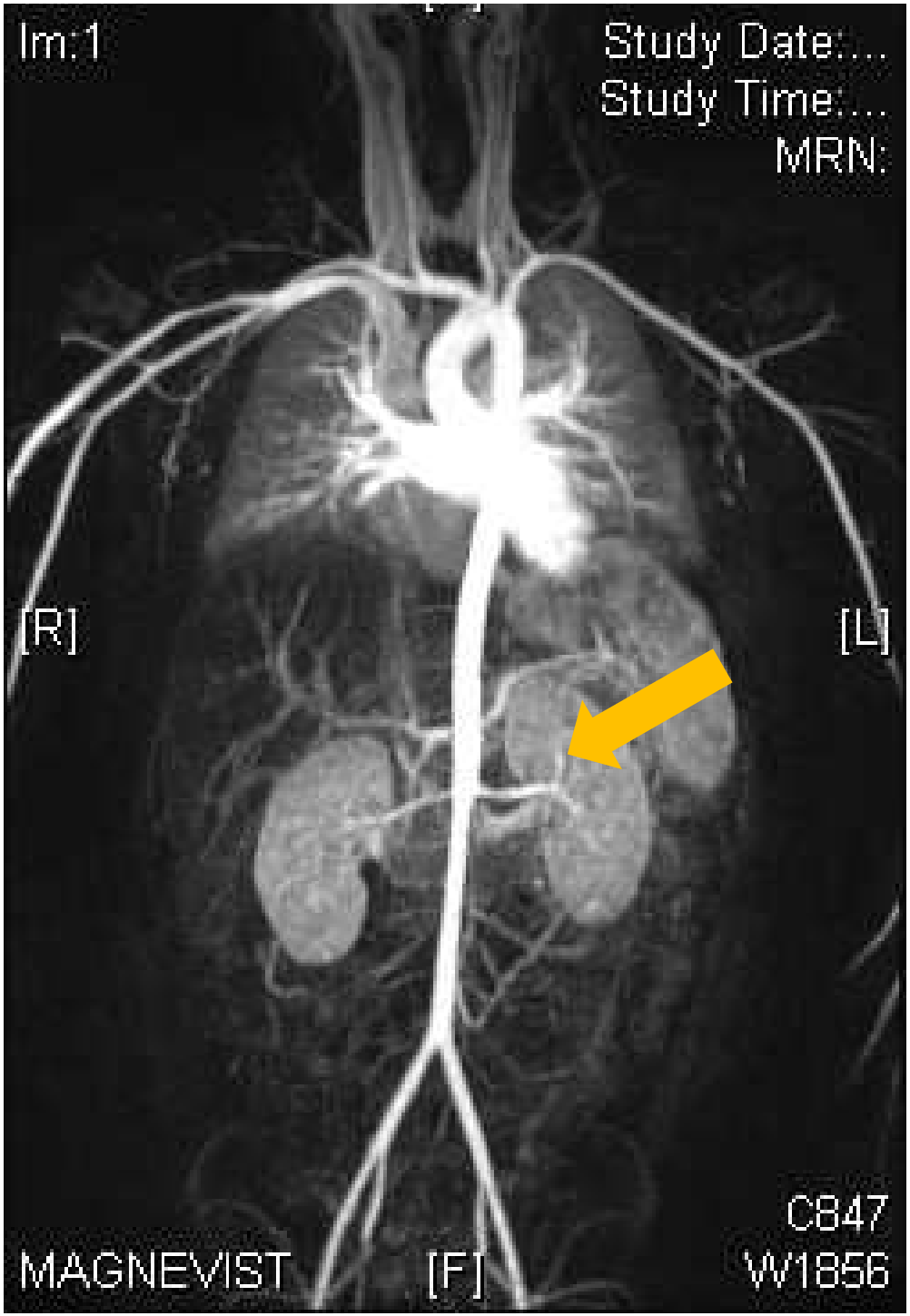


MRA

- 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

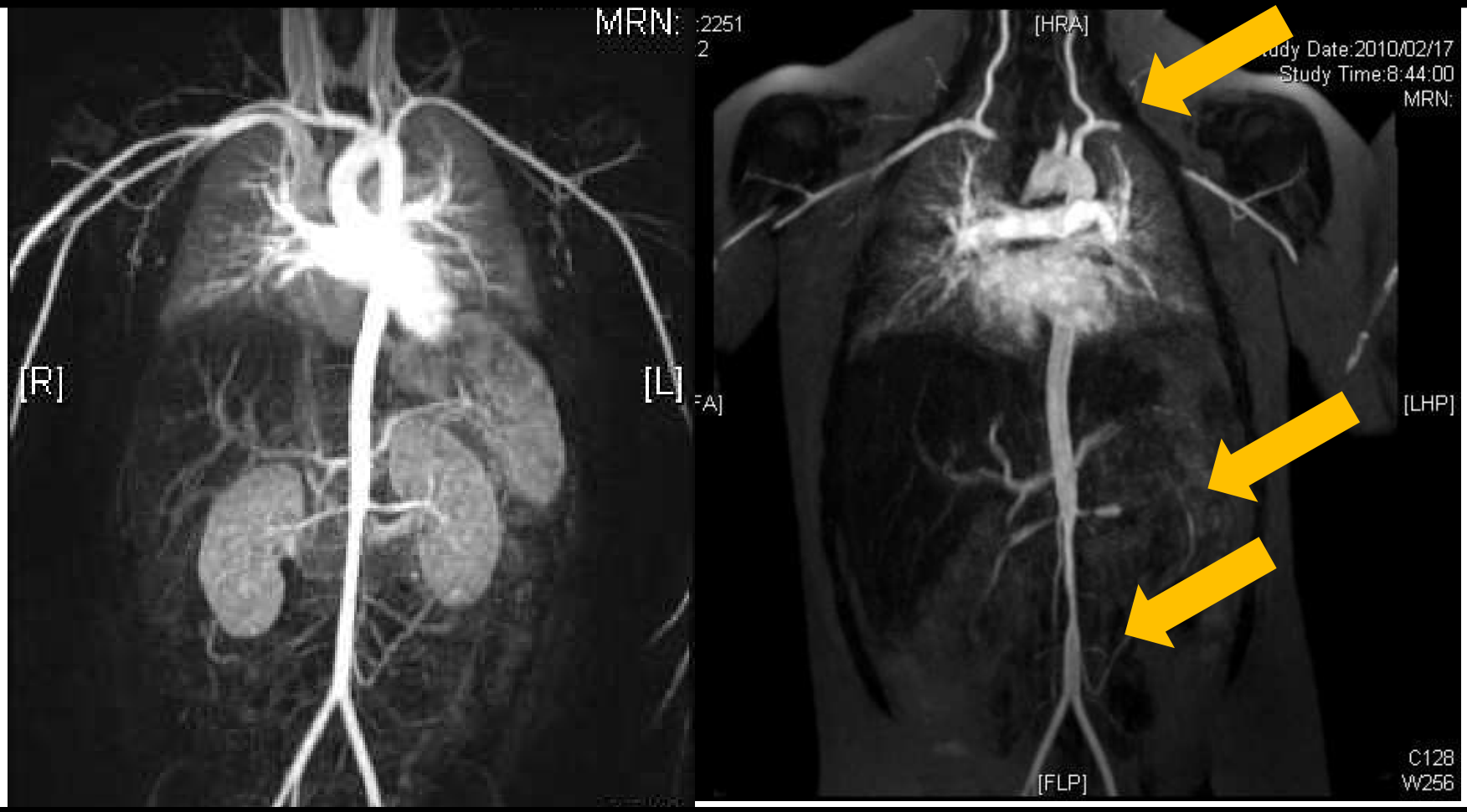
- Improvement of the focal renal artery stenosis
- Stable appearance of enhancing vessel wall thickening of SMA and branches

Treatment October 2009-Febuary 2010

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

October 2009

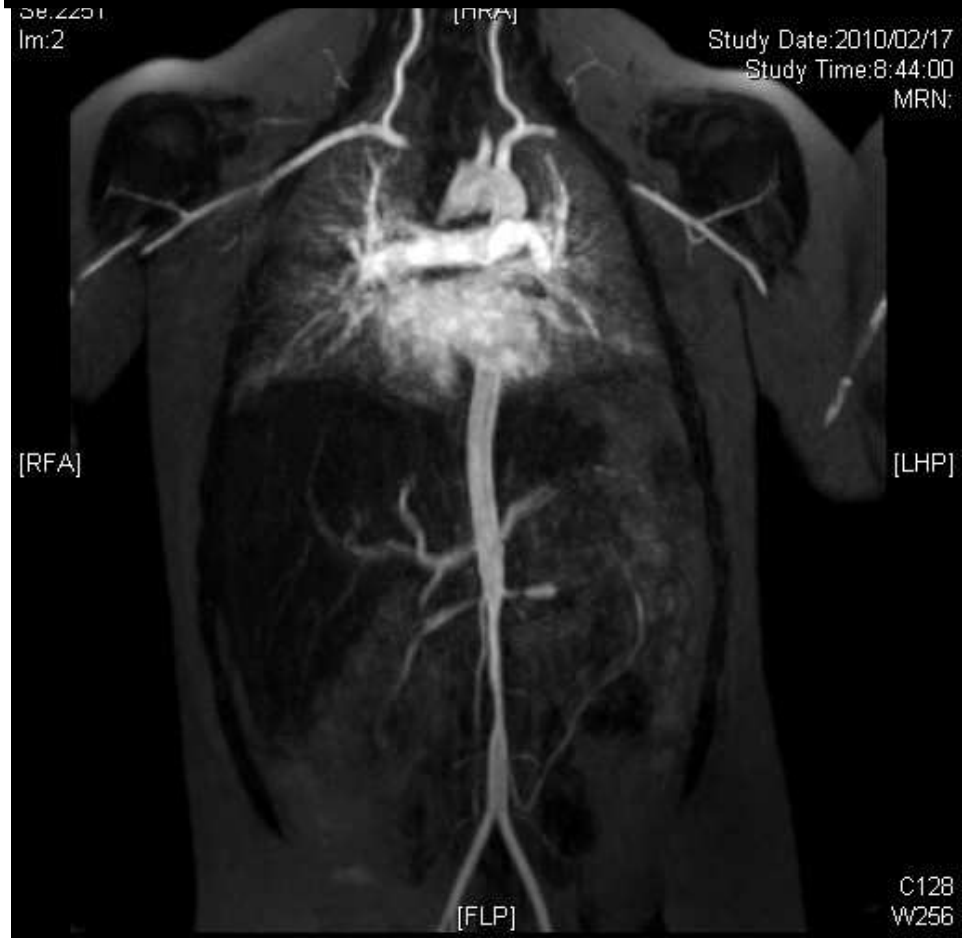
February 2010



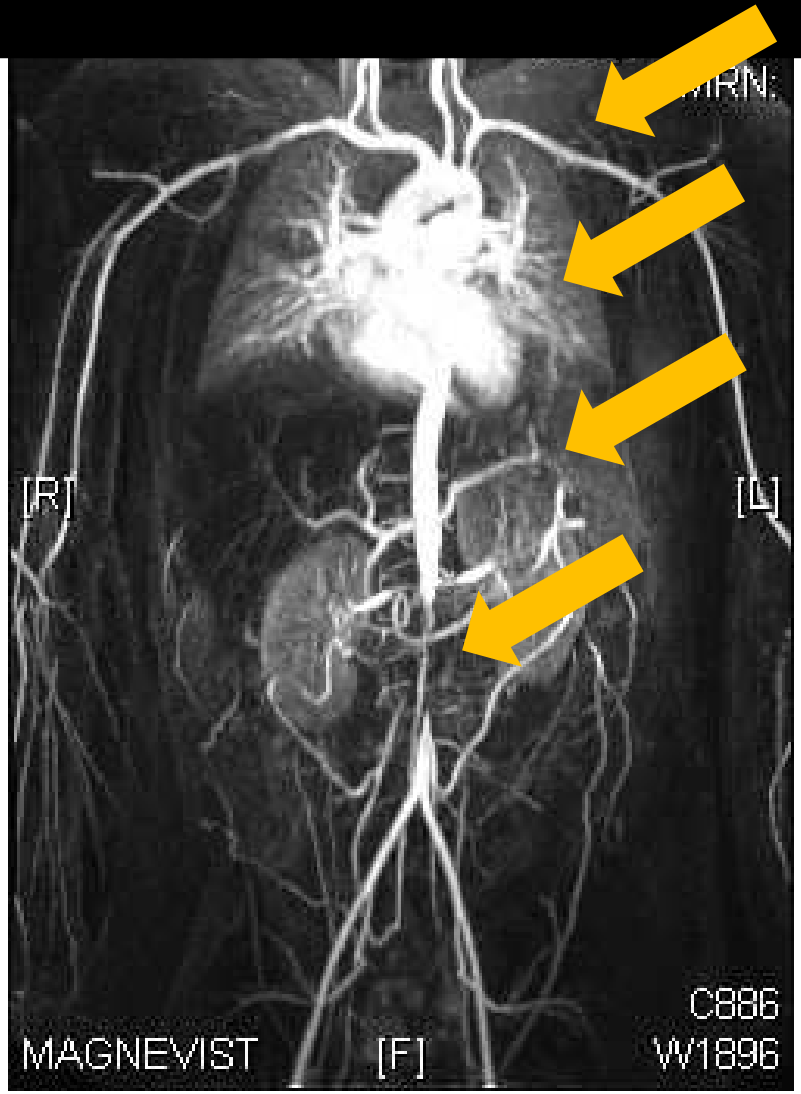
Treatment February-May 2010

- "Infliximab rescue therapy" 5mg/kg monthly IV in addition
- Methotrexate 1 mg/m2 /week
- Corticosteroids (10mg)
- Enoxaparin

February 2010



May 2010

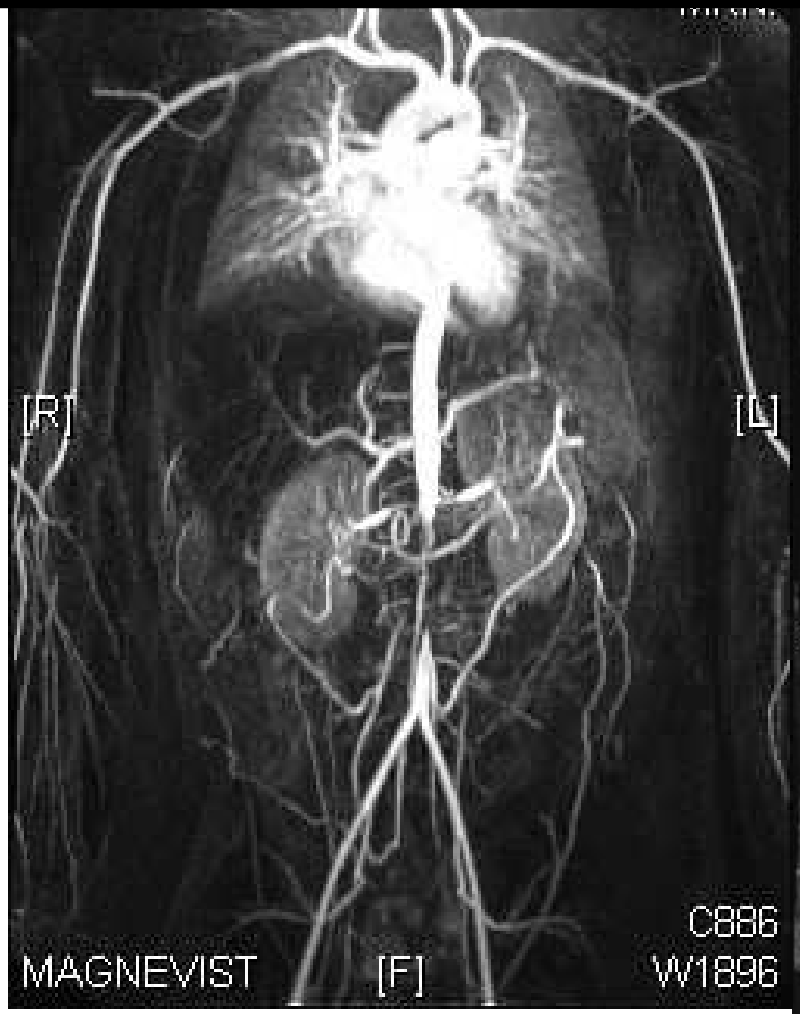


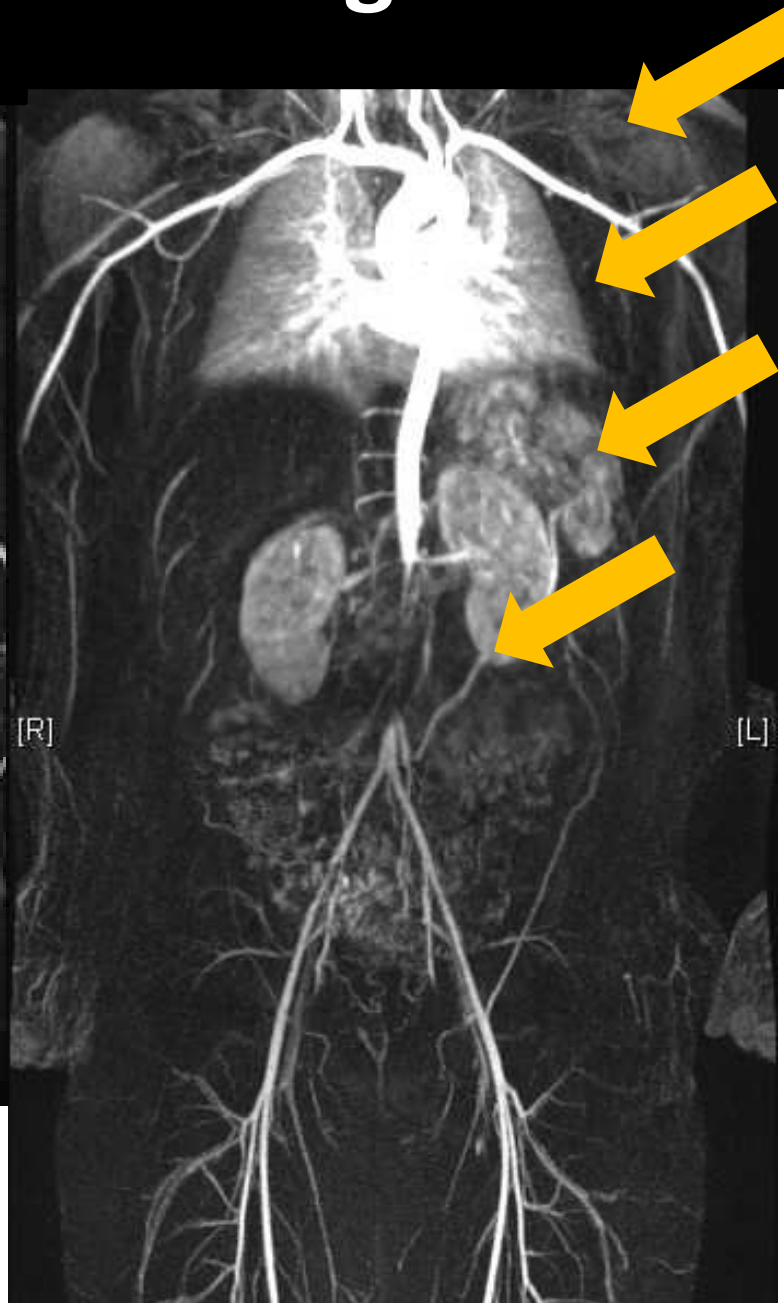
Treatment May-August 2010

- Daily oral cyclophosphamide (50mg/day, 2mg/kg) plus high dose corticosteroids (60mg/day)
- Enoxaparin

May 2010

August 2010



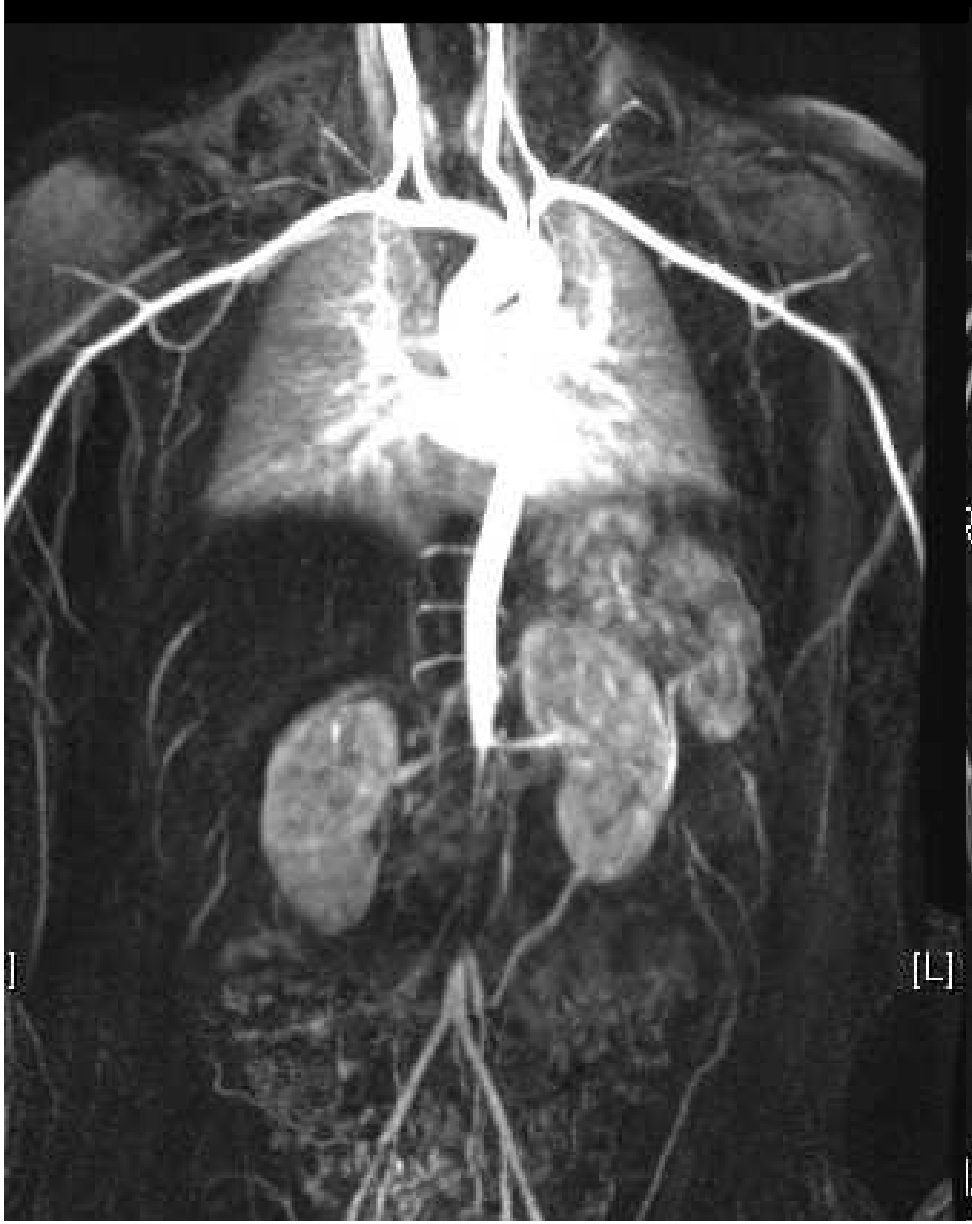


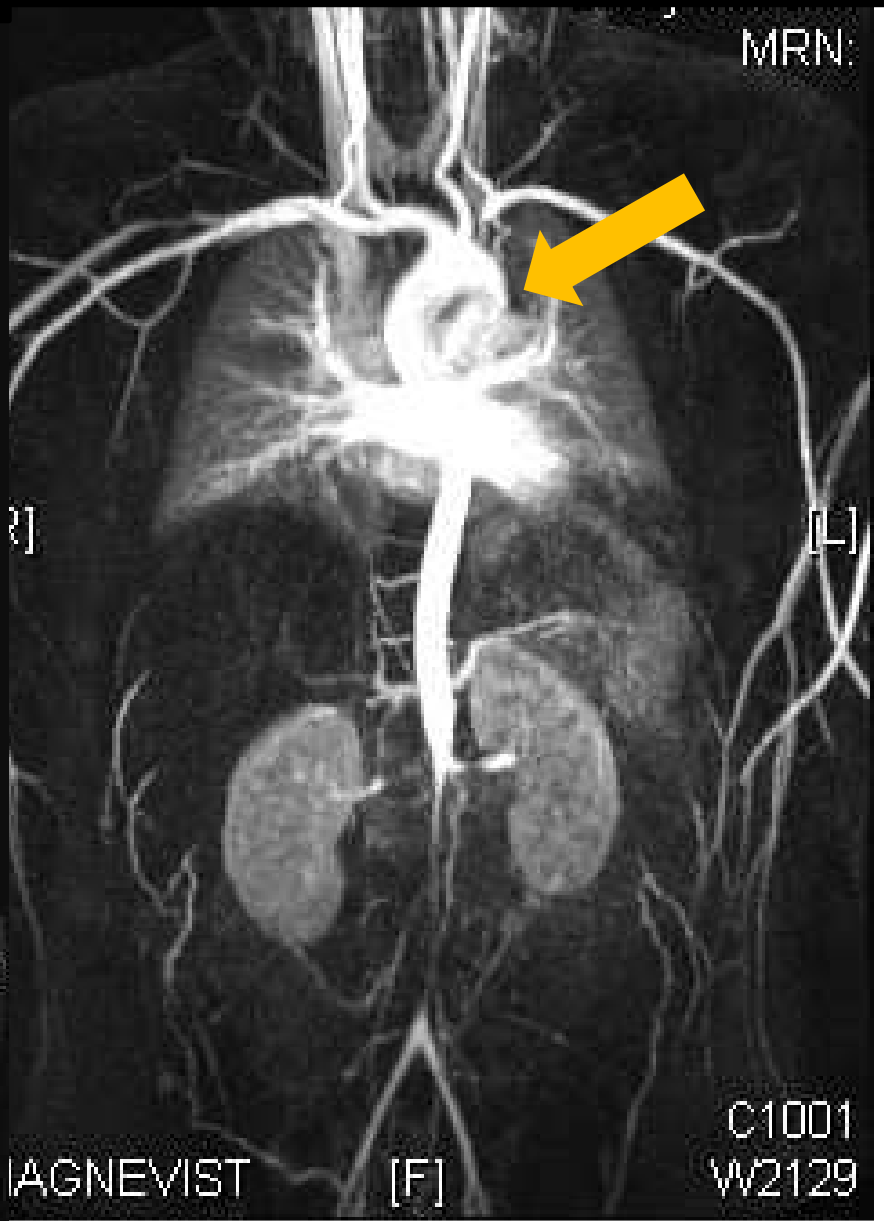
Treatment August 2010-Febuary 2011

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

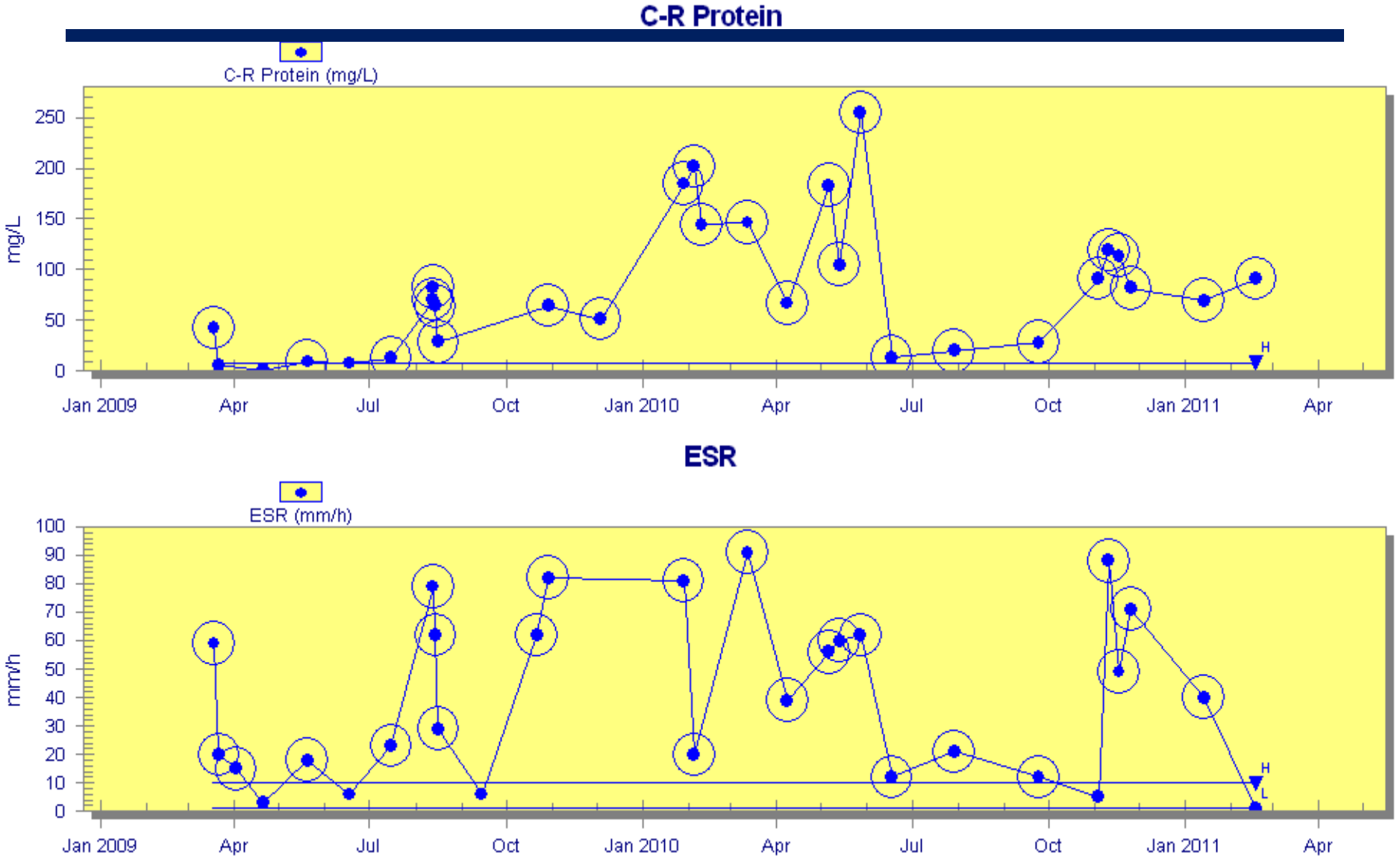
August 2010

Feb 2011





Inflammatory markers



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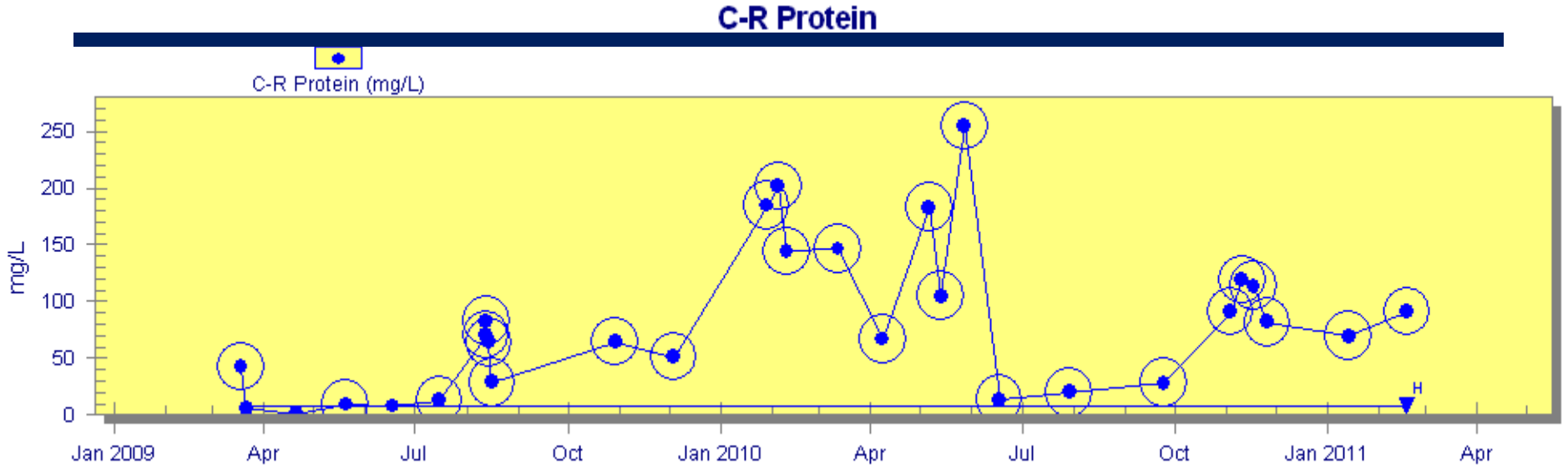

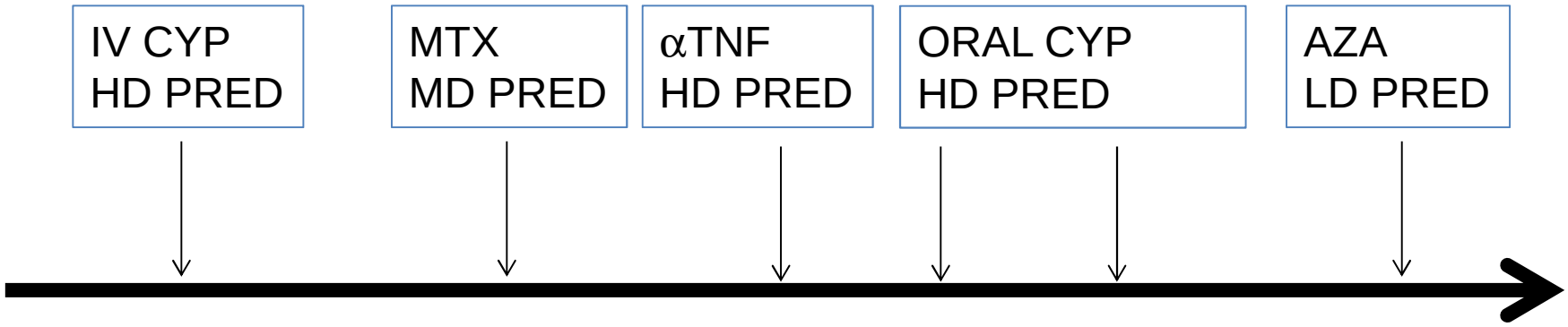

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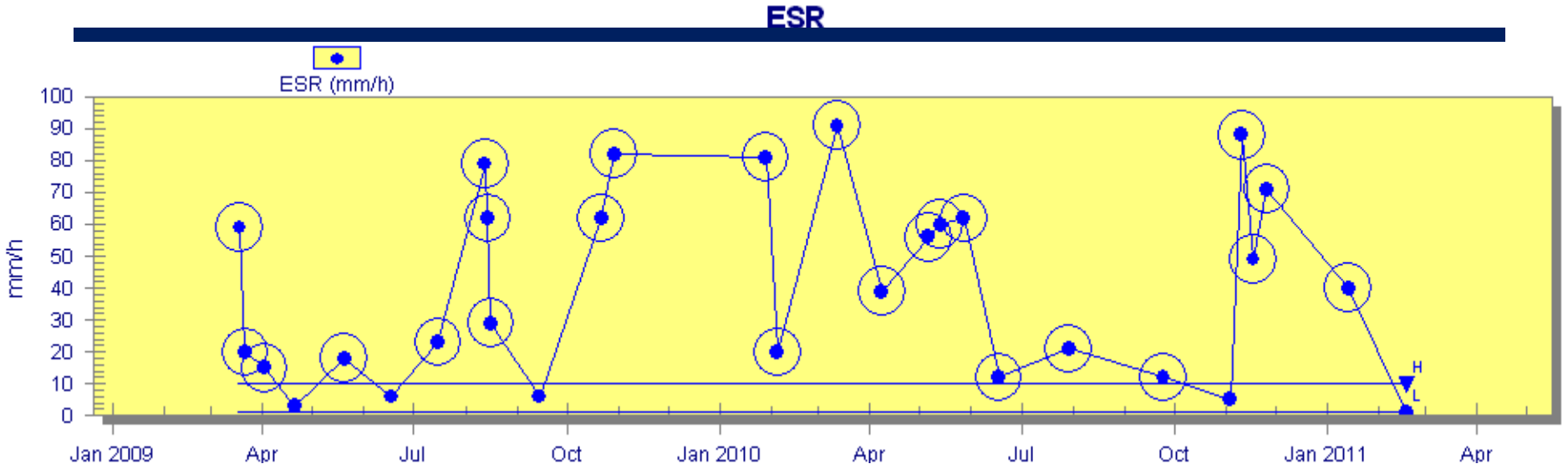
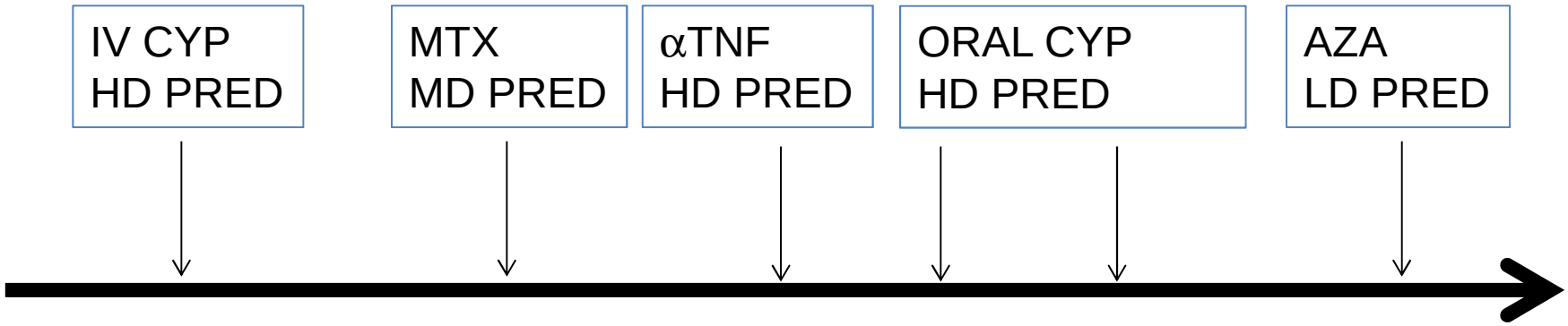
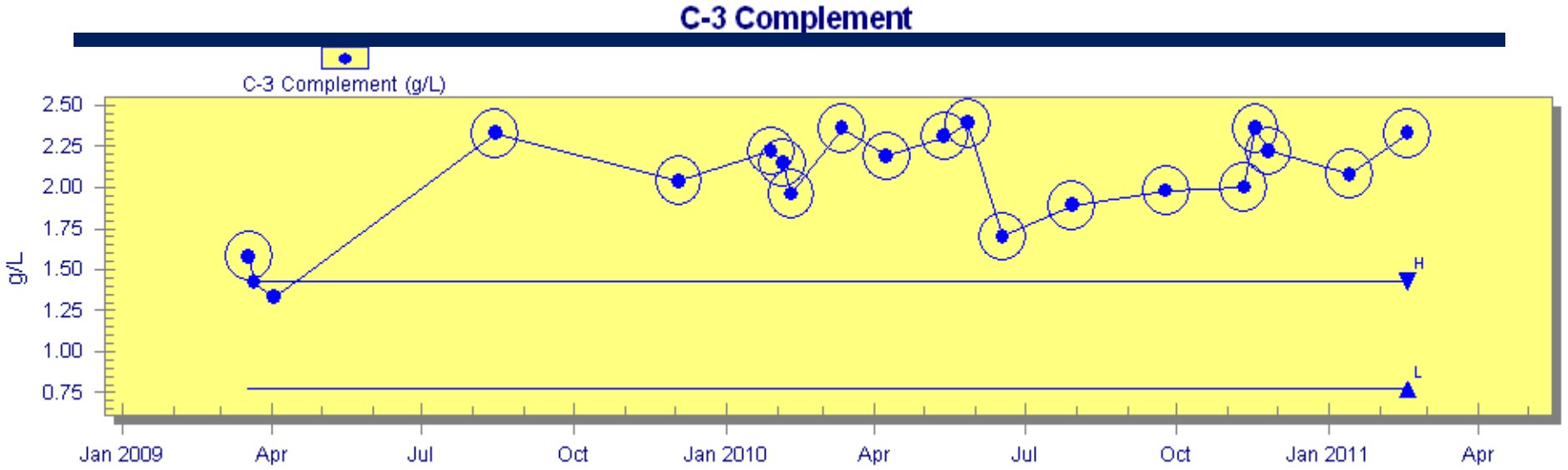
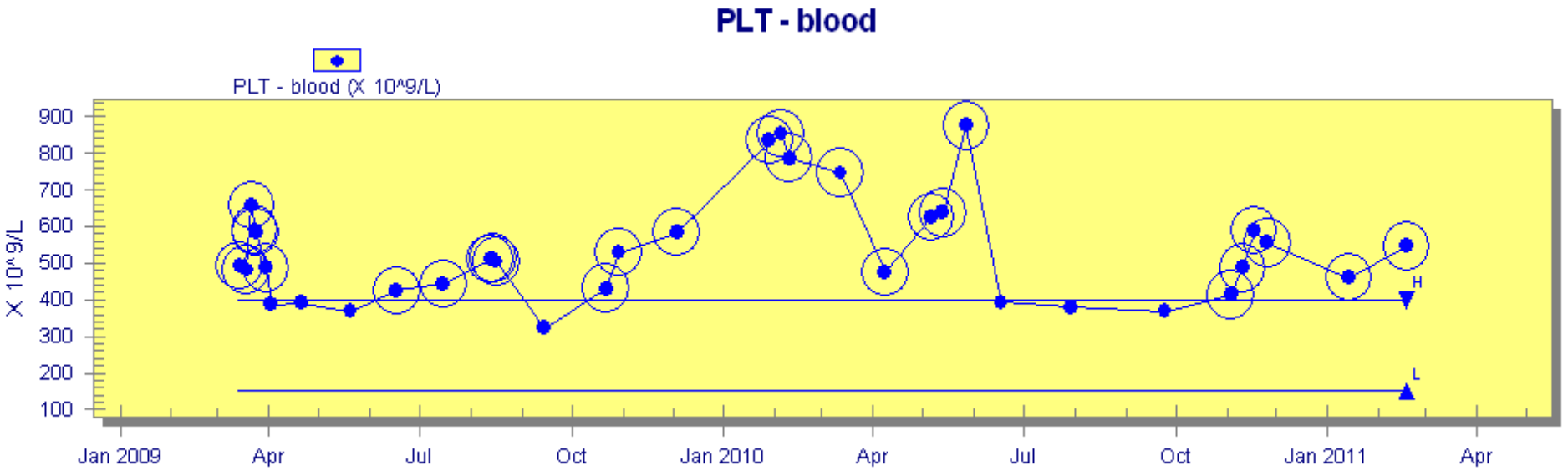




Inflammatory markers

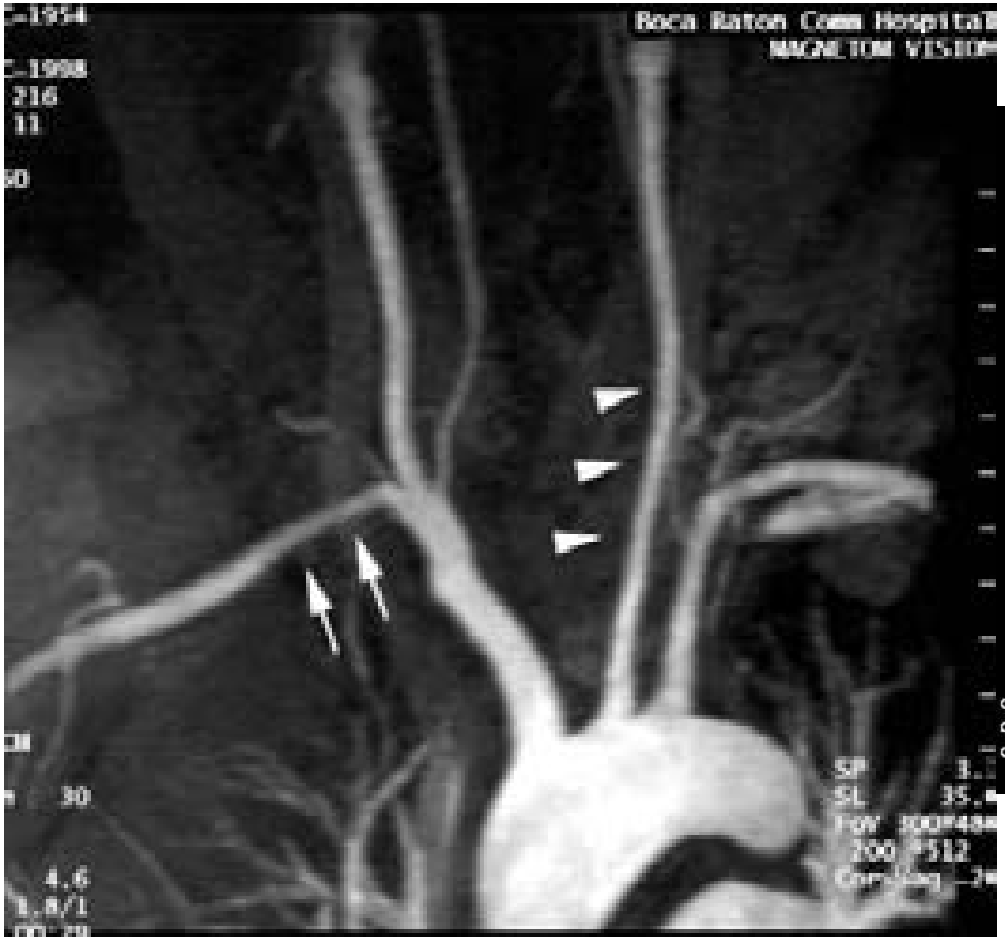


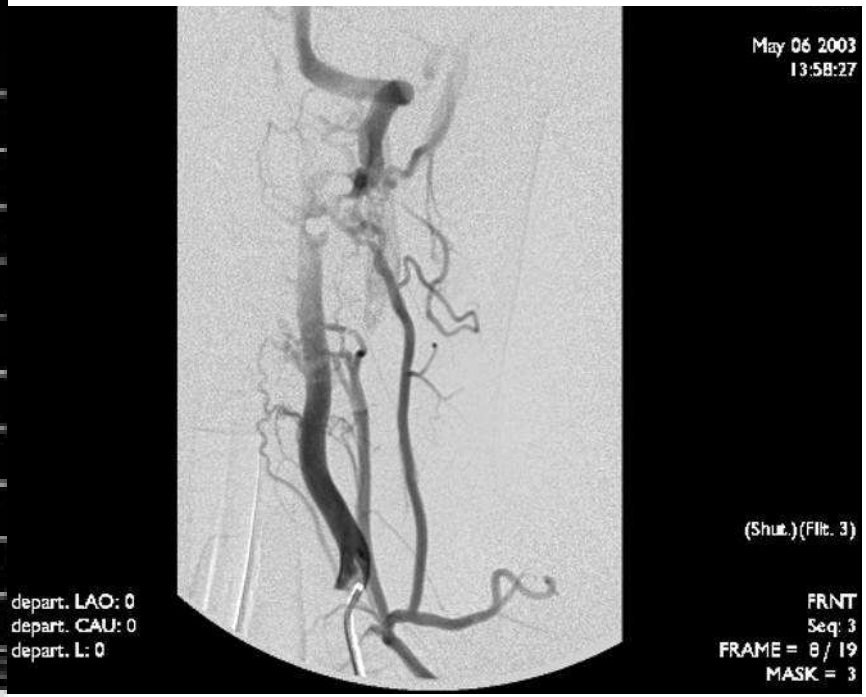


Treatment March 2012

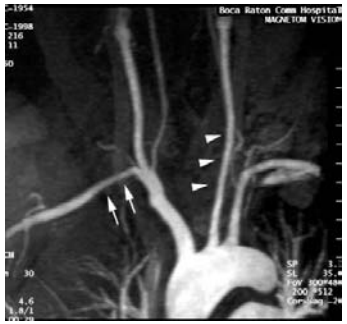
- Off Prednisone, on Imuran maintenance
- MRA stable, clinically claudication
- Exposure to 6 months of IV and 10 month of oral cyclophosphamide (cumulative dose: 17g)
- Moderate to high dose corticosteroids for 24 months (vertebral fractures, cataracts)

Large vessel vasculitis





Takayasu arteritis



Takayasu arteritis PRES/EULAR 2005

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:

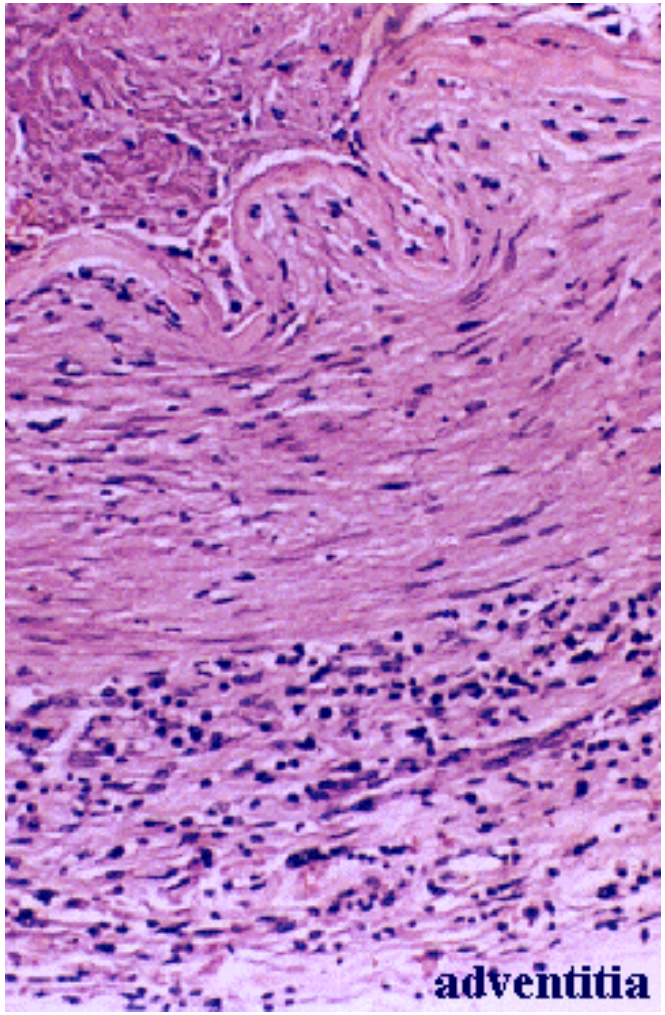
- Decreased peripheral artery pulse(s) and/or claudication of extremities
- Blood pressure difference >10 mm Hg
- Bruits over aorta and/or its major branches
- Hypertension (related to childhood normative data)

CT, computed tomography; MR, magnetic resonance.

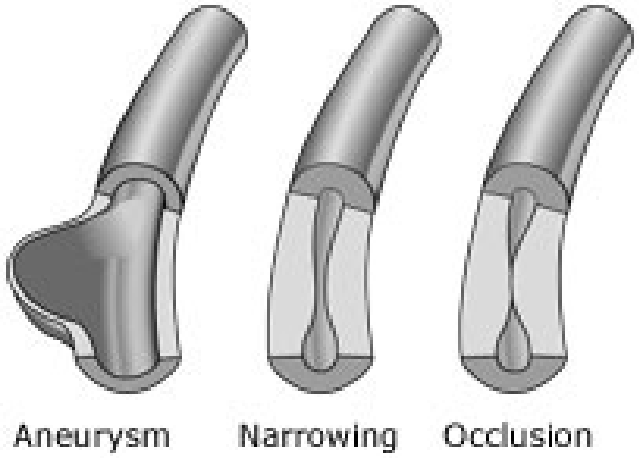
Diagnosis TA: Angiography positive plus at least one criterion

Ozen, ANR 2005

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 Guillevin,[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 I 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

Statement	Level of evidence	Median final vote
We recommend a thorough clinical and imaging assessment of the arterial tree when a diagnosis of Takayasu arteritis is suspected	3	C
A temporal artery biopsy should be performed whenever a diagnosis of giant cell arteritis is suspected, but this should not delay the treatment; a contralateral biopsy is not routinely indicated	3	C
We recommend early initiation of high-dose glucocorticoid therapy for induction of remission in large vessel vasculitis	3	C
We recommend that an immunosuppressive agent should be considered for use in large vessel vasculitis as adjunctive therapy	1A for GCA	B for GCA
	3 for TAK	C for TAK
Monitoring of therapy for large vessel vasculitis should be clinical and supported by measurement of inflammatory markers	3	C
We recommend the use of low-dose aspirin in all patients with giant cell arteritis	3	C
Reconstructive surgery for Takayasu arteritis should be performed in the quiescent phase of disease and should be undertaken at expert centres	3	C

EULAR, European League Against Rheumatism; GCA, giant cell arteritis; TAK, Takayasu arteritis.

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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

Wallis. Semin Arthritis Rheum.2005;34:34-8
Park. Rheumatology. 2006;45:545-8
Tripathy. Clin Immunol 2006;118:154-8

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

Molloy. Ann Rheum Dis. 2008;67:1567-69

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)

Agent	No. (%)	Duration of therapy* in months, median (range)	Maximum dose, median (range)
Methotrexate	22 (88)	9 (1–144)	20 mg/week (15–27.5)
Cyclophosphamide	10 (40)	6 (1–12)	150 mg/day (50–150)†
Azathioprine	5 (20)	16 (1–48)	150 mg/day
Mycophenolate mofetil	3 (12)	4 (1–4)	2 g/day (2–3)
Ciclosporine A	2 (8)	3	100 mg twice a day
Tacrolimus	2 (8)	4	6 mg/day

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.

Molloy. Ann Rheum Dis. 2008;67:1567-69

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

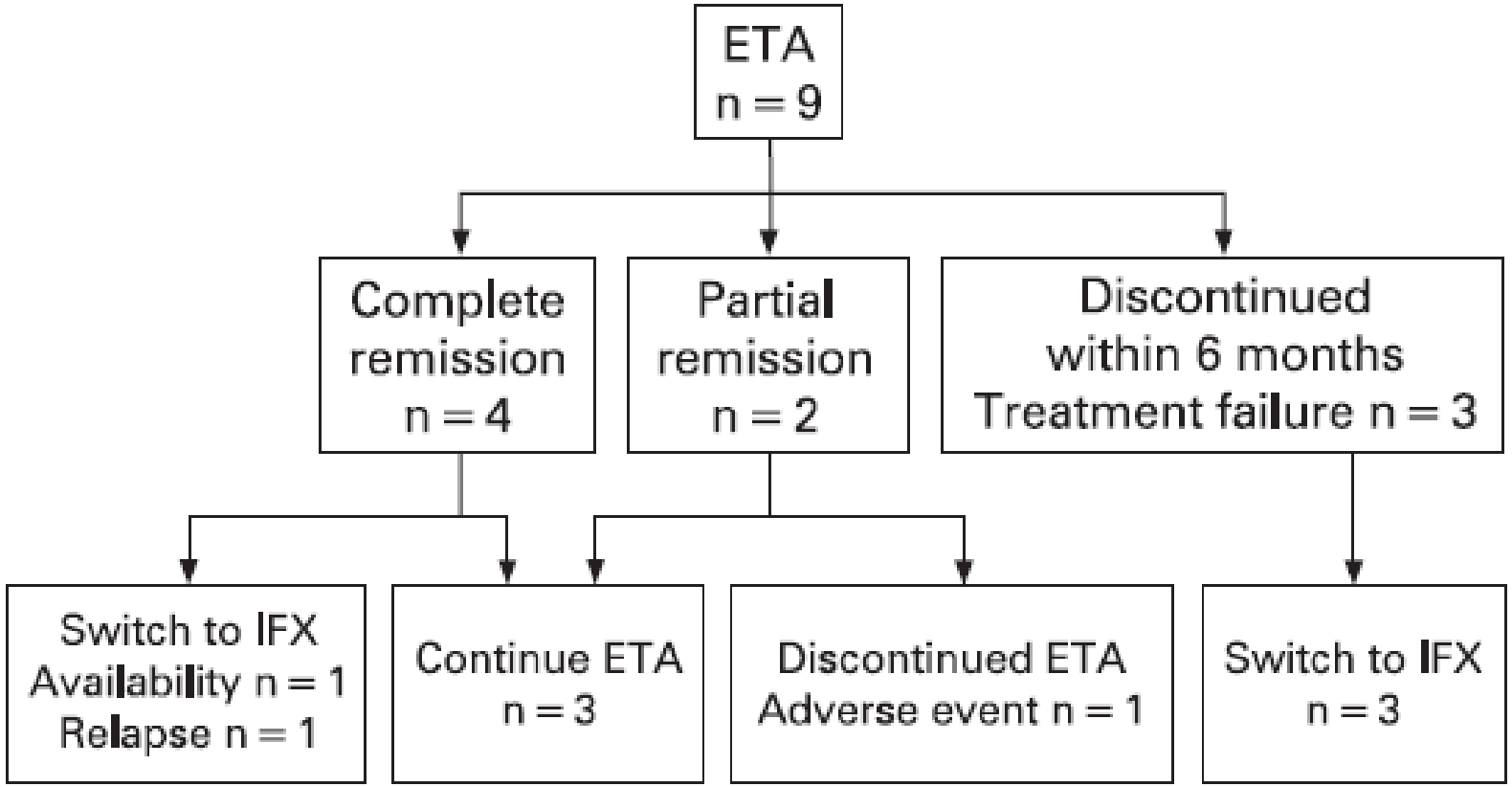


Figure 1 Outcome of treatment of refractory patients with Takayasu arteritis (TAK) with etanercept (ETA). IFX, infliximab.

Outcome Infliximab

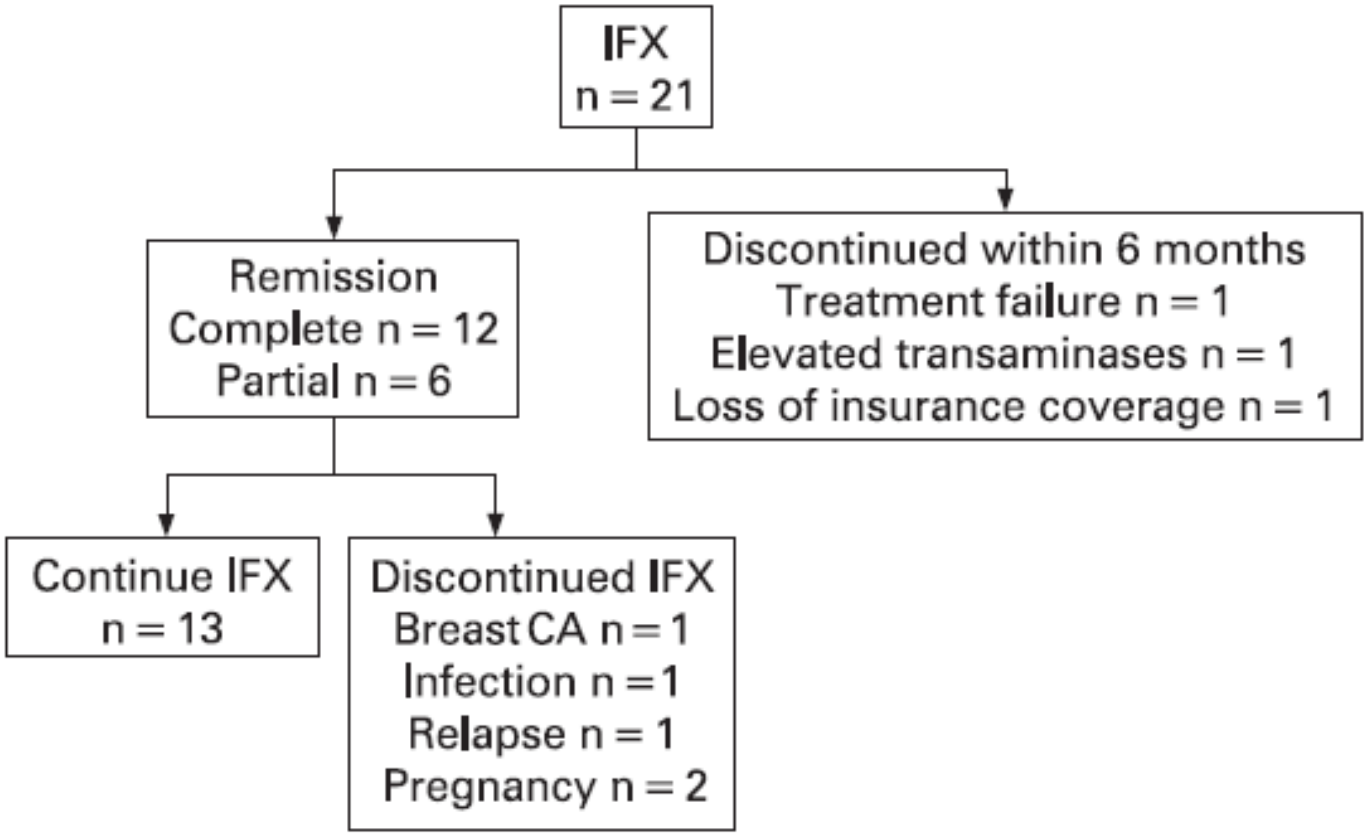


Figure 2 Outcome of treatment of refractory patients with Takayasu arteritis (TAK) with infliximab (IFX).

Prednisone therapy

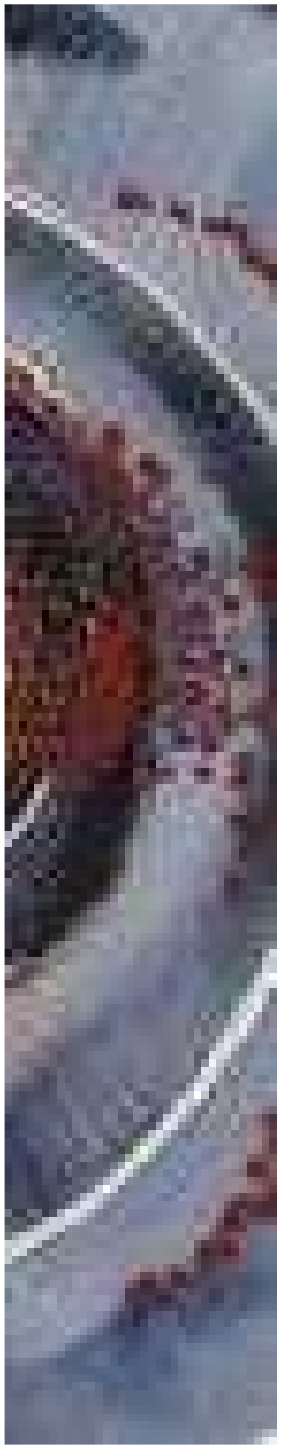
- Discontinued in 60%
  - After a median interval of 10 months (range 0-72)
  - Prednisone-free remission maintained for a median duration of 30 months (range 6-82)
- Tapered <10mg/day in 28%

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

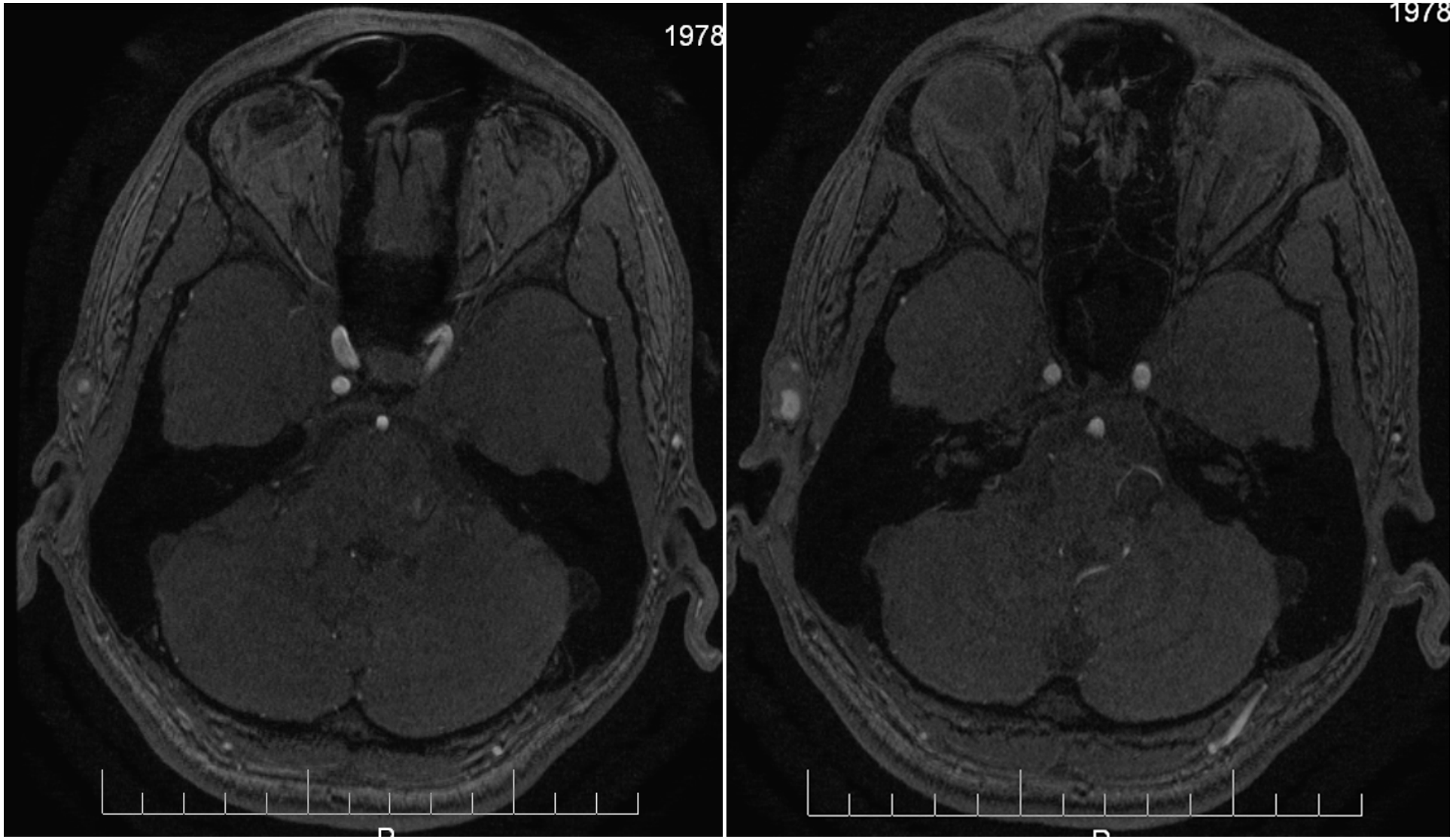
- No family history
- Minor asthma (salbutamol puffs, PRN)
- Married, 4 healthy children
- Smoker (5 packs-year)

- 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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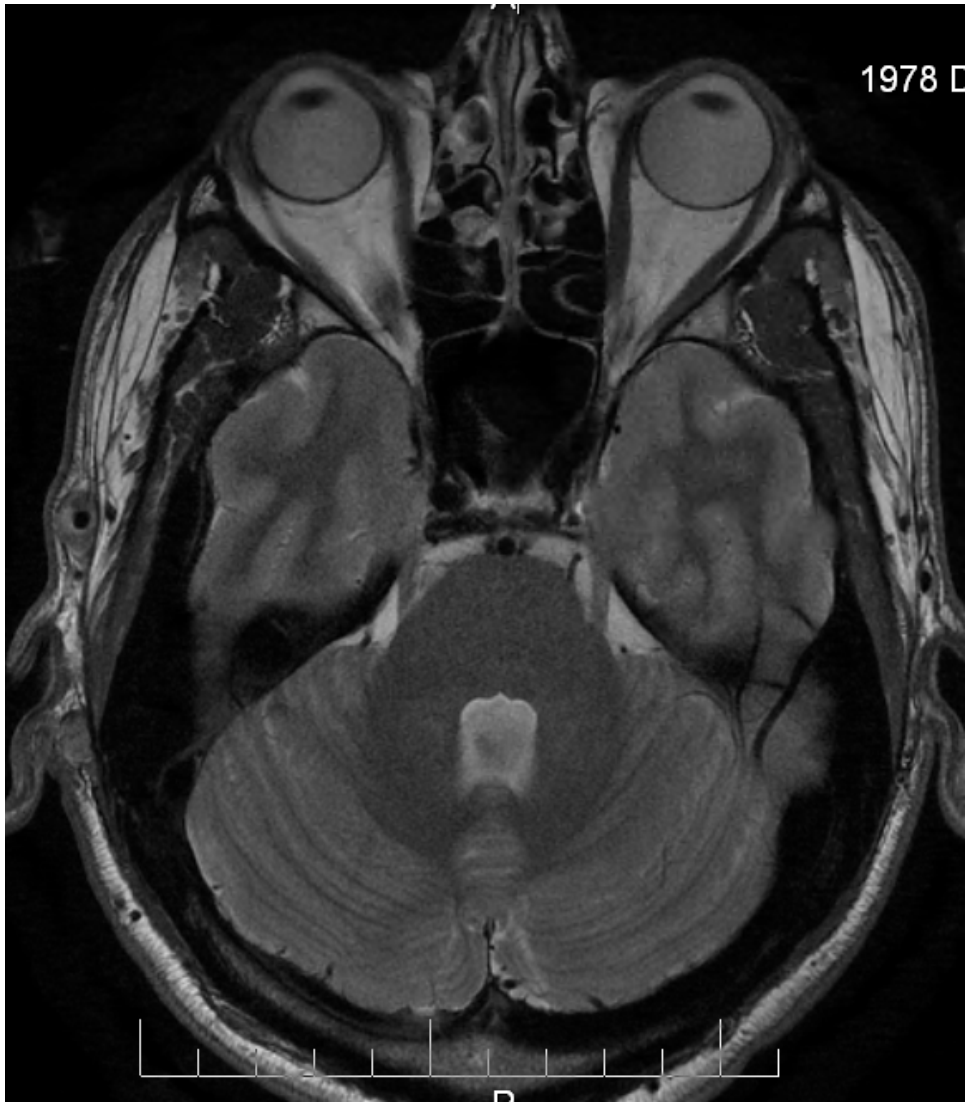
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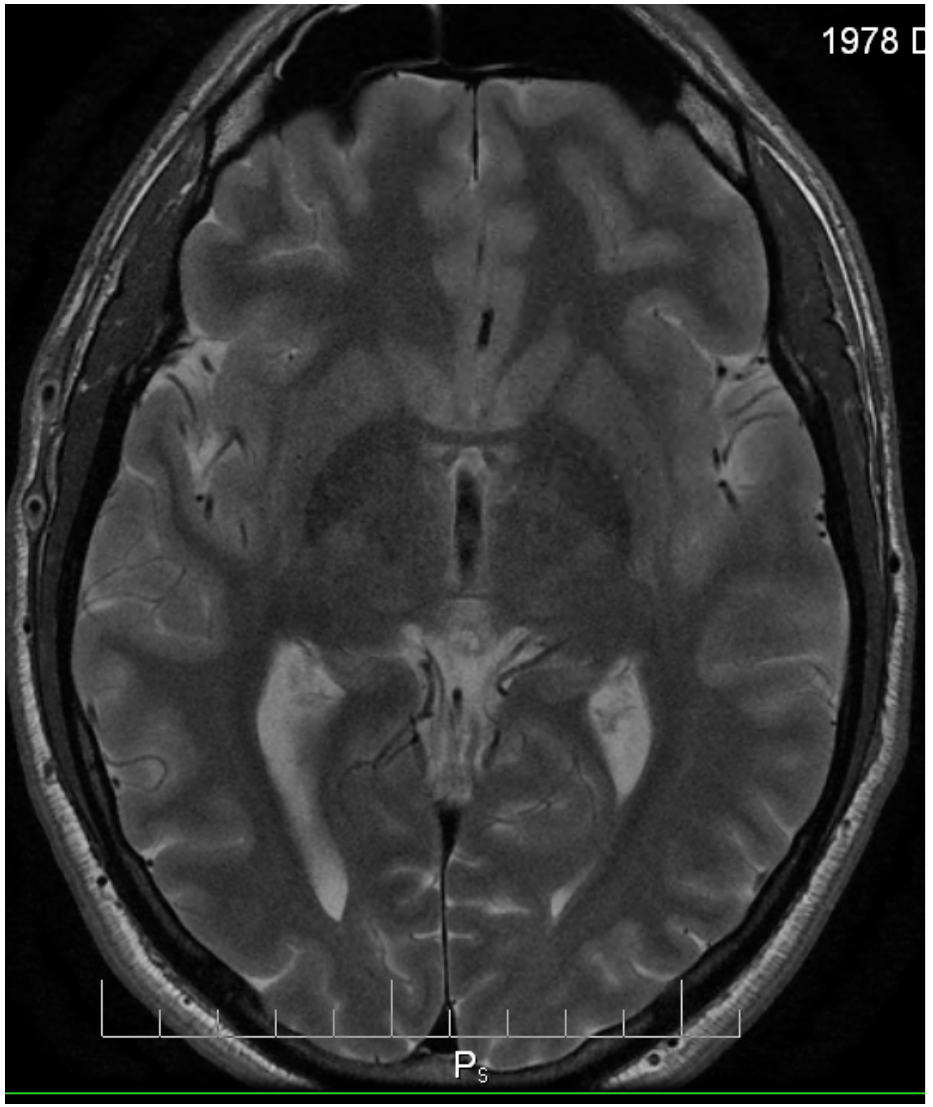
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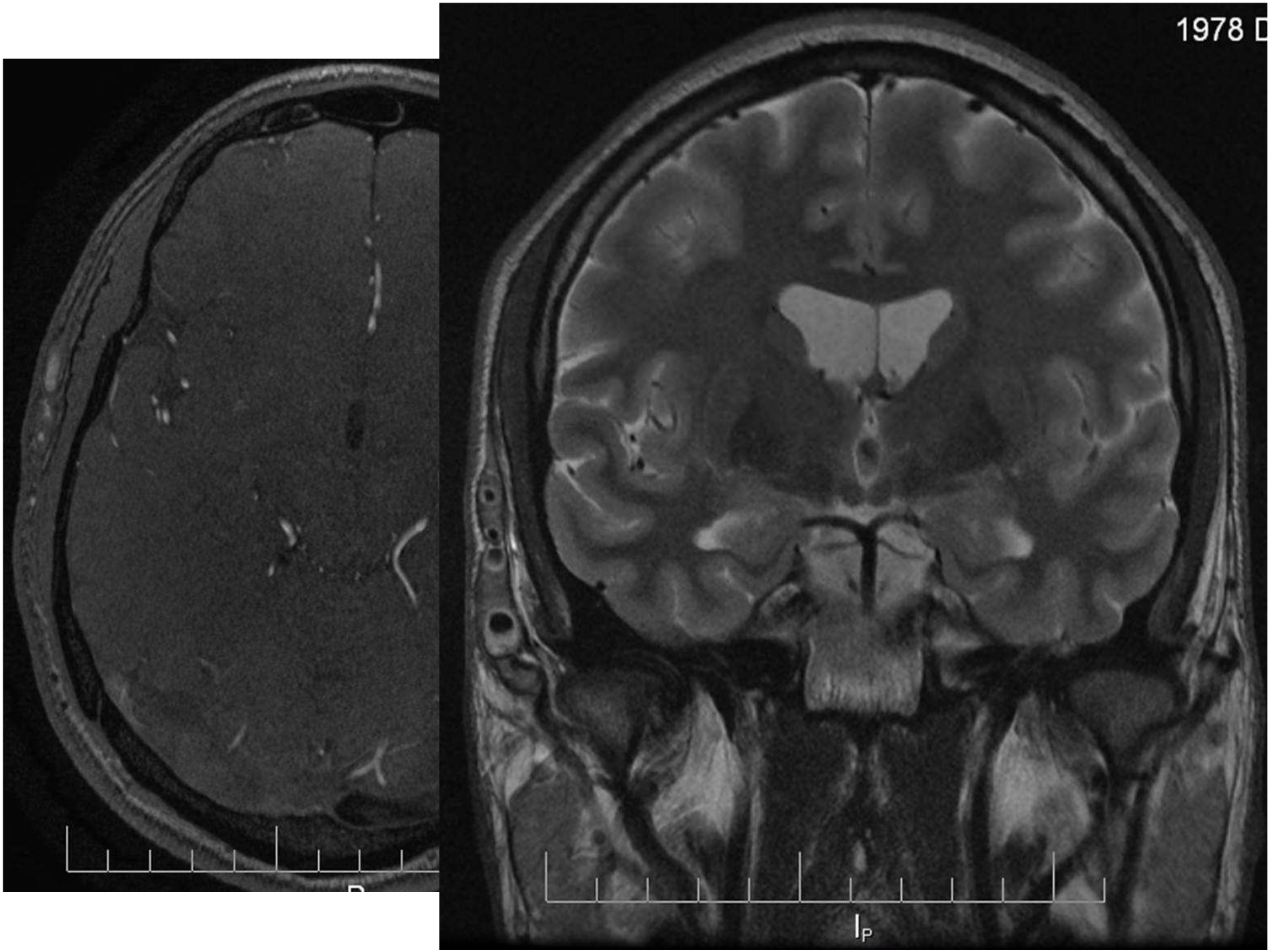
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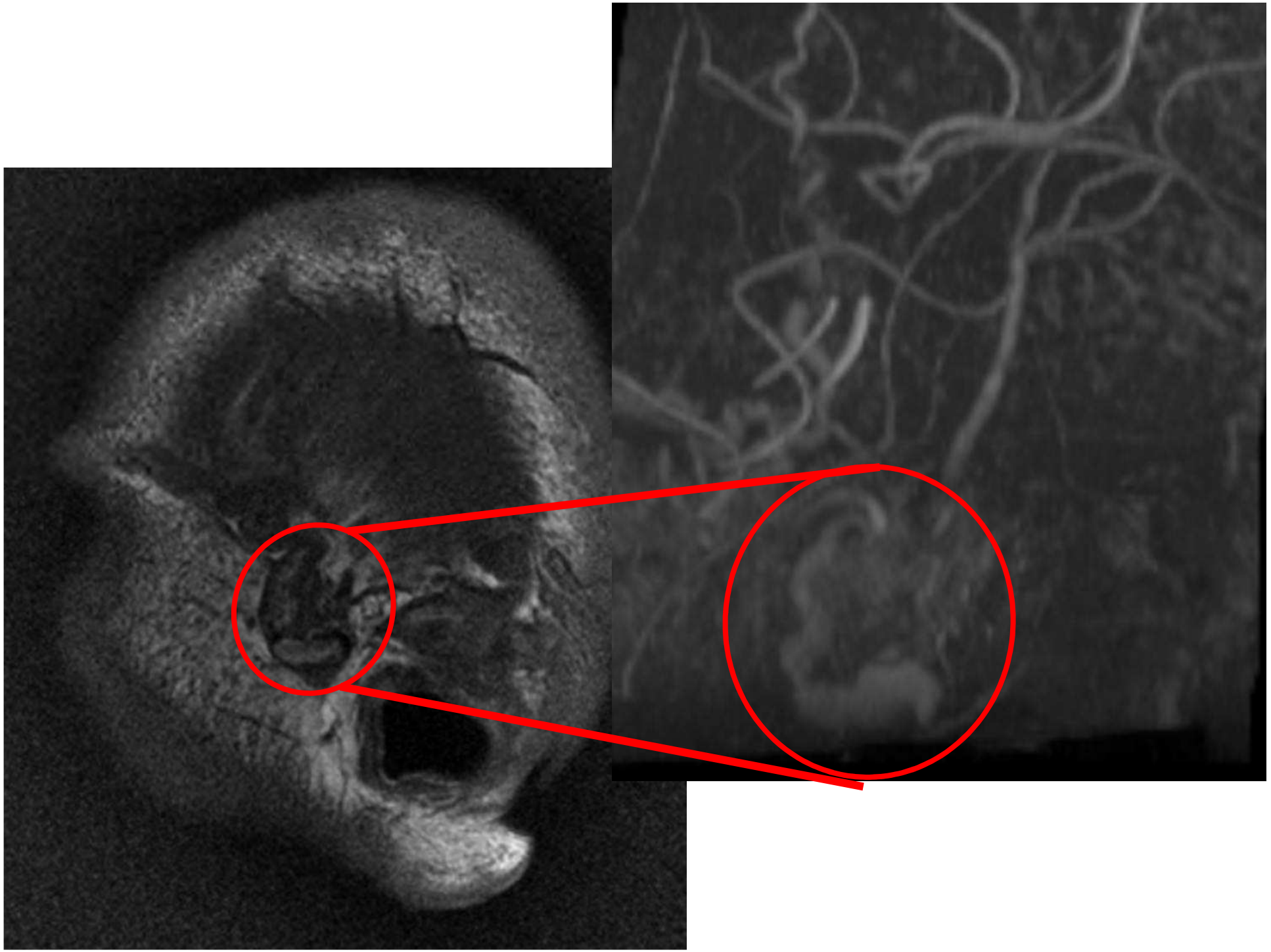

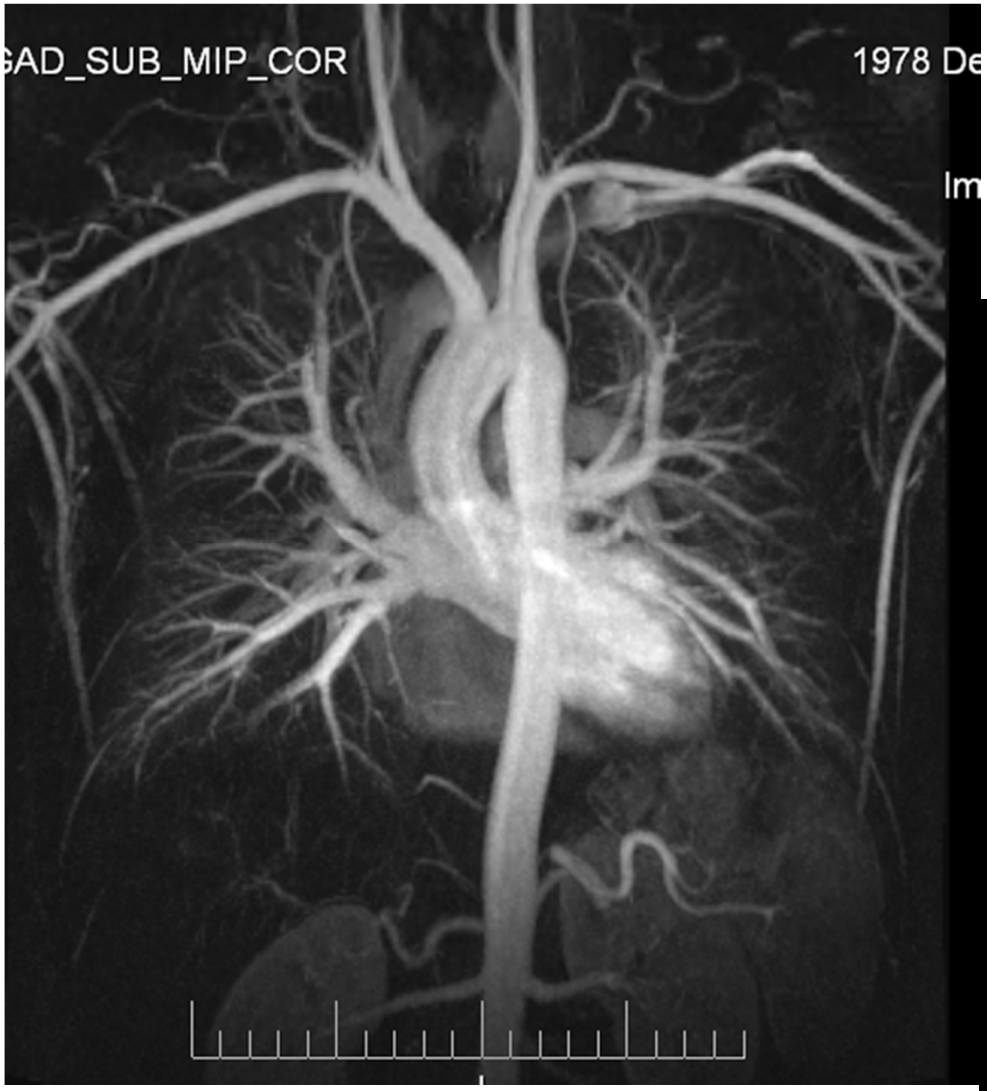
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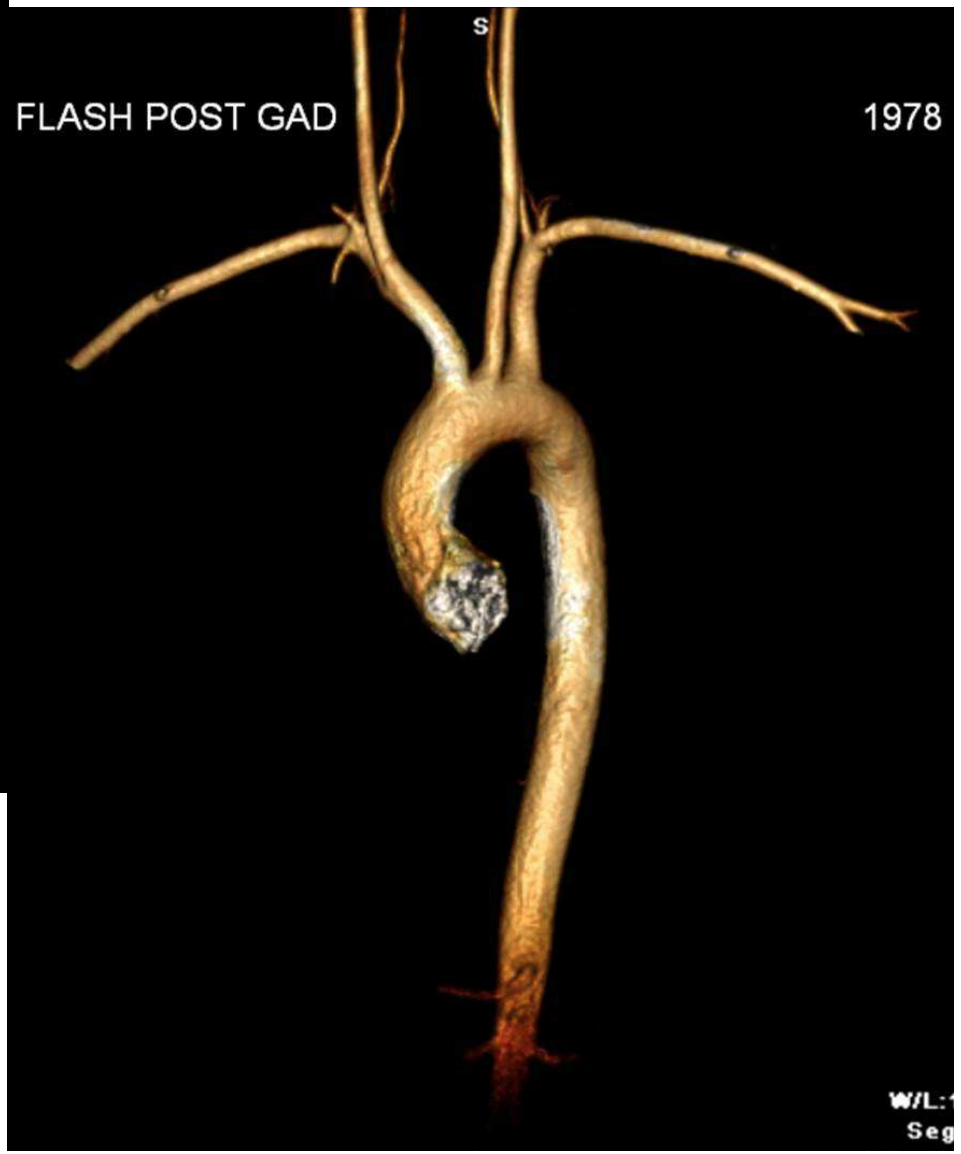
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W/L:
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Christian, 32 years-old

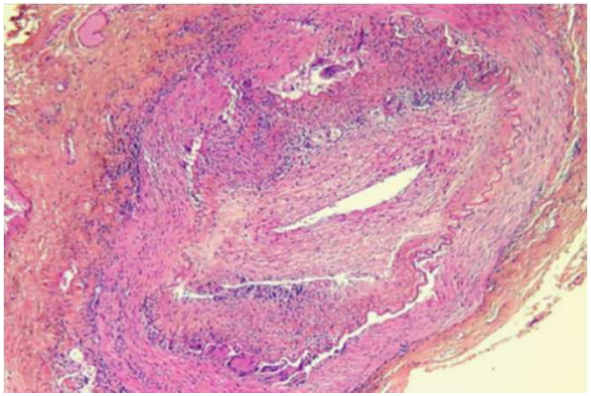
- Diagnosis?
  1. « Temporal Takayasu? »
  2. « GCA/LVV of the youth? »
  3. Other systemic vasculitis with TA involvement?
  4. TA fibromuscular dysplasia?
  5. Ehlers-Danlos (type IV)?
  6. Other?
- Biopsy?
- Treatment?

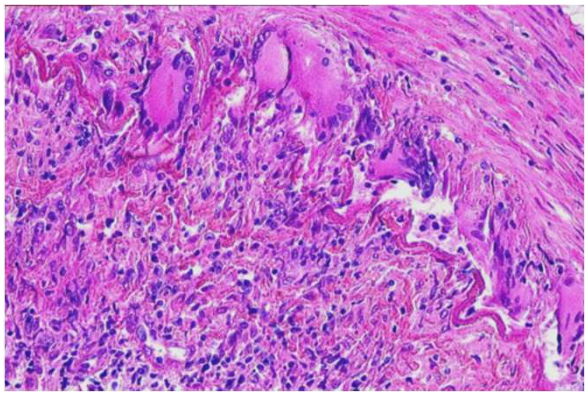
ACR criteria as the silver standard…

1. Age ≥ 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 → sensitivity 93.5%, specificity 91.2%





Hunder et al. Arthritis Rheum 1990;33:1122-8

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%

Bloch et al. Arthritis Rheum. **1990** Aug;33(8):1068-73.

Ehlers-Danlos Syndrome Type IV

- Hereditary, DA, with *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

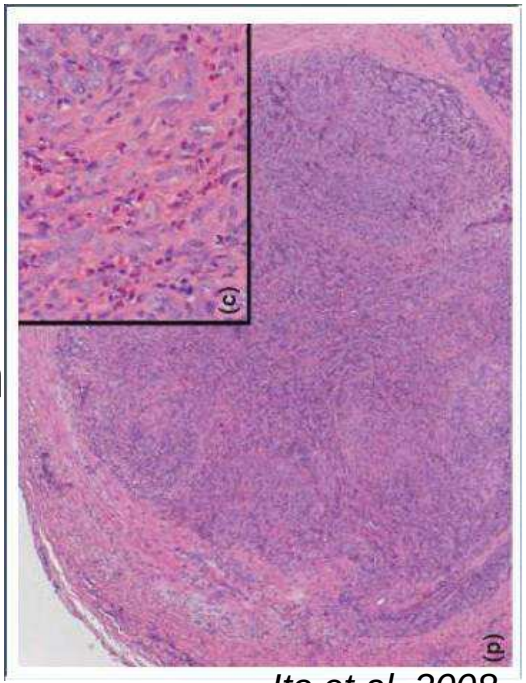
Christian, 32 years-old

- 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

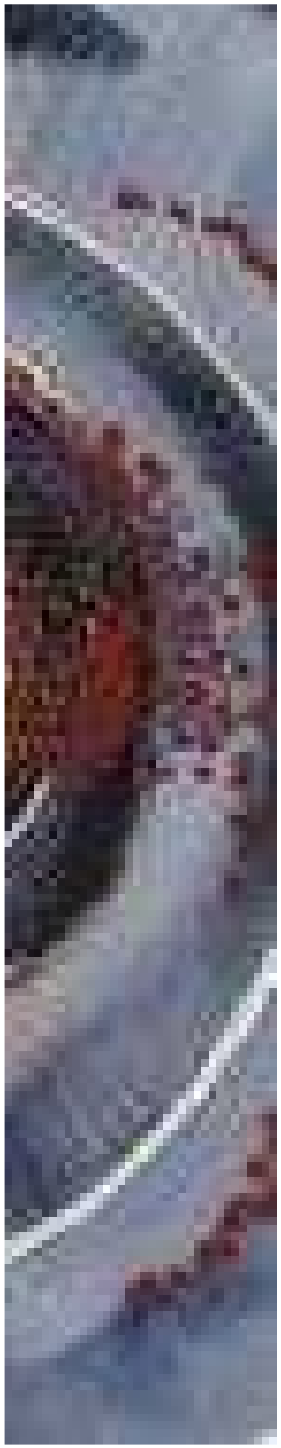
Tomlinson et al. Mayo Clin Proc 1994

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



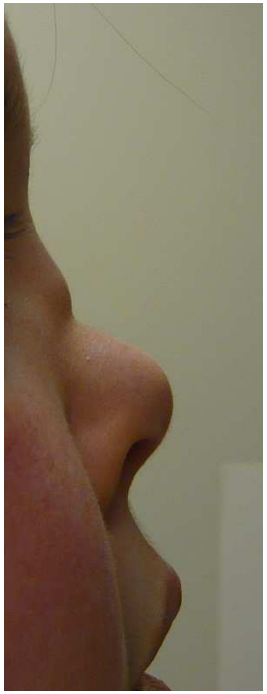
Izeult, 32 years-old

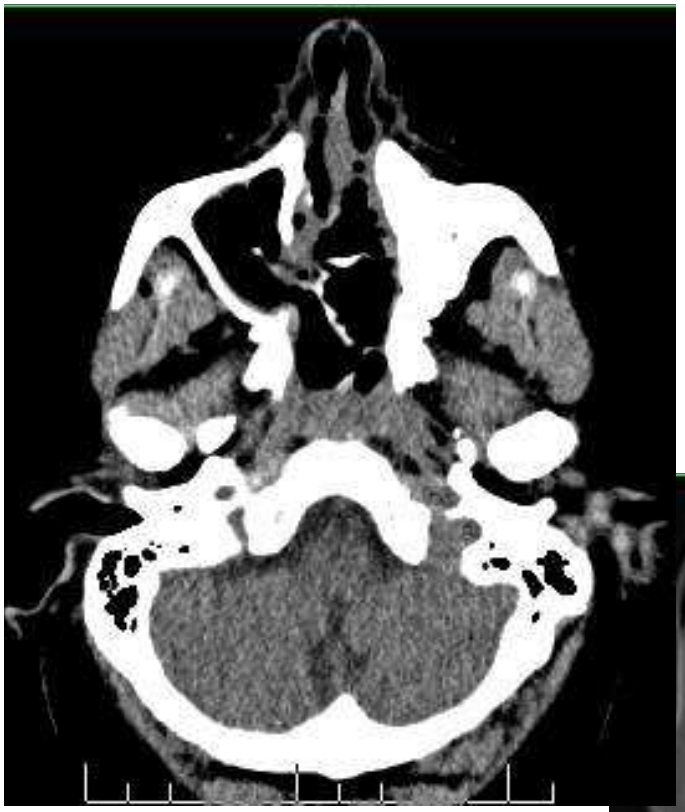
- Married, no children
- No significant medical history

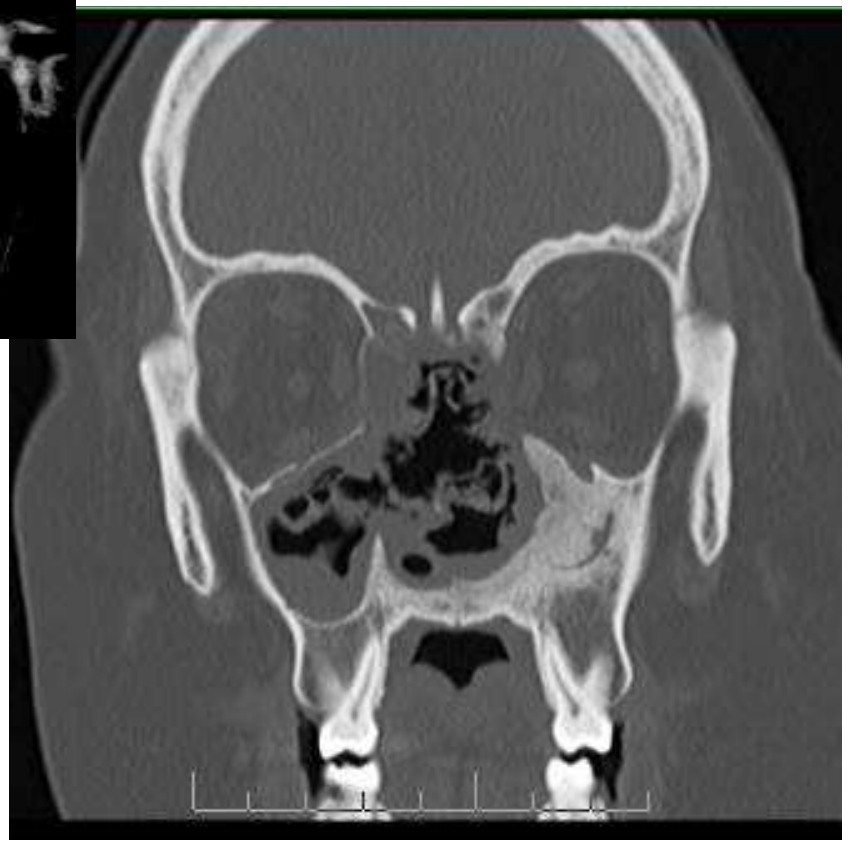
- Sinusitis since 1994 (14 years-old)
- 1996: saddle-nose deformity

  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

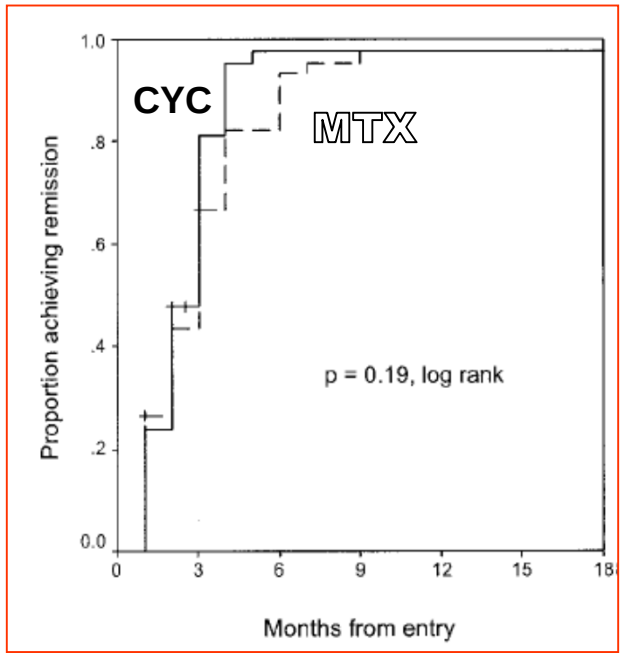
- Methotrexate vs oral Cyclophosphamide for induction
- Non-inferiority trial (d=15%) for remission at 6 months
- 100 p. with “early systemic” GPA **for 12 months**

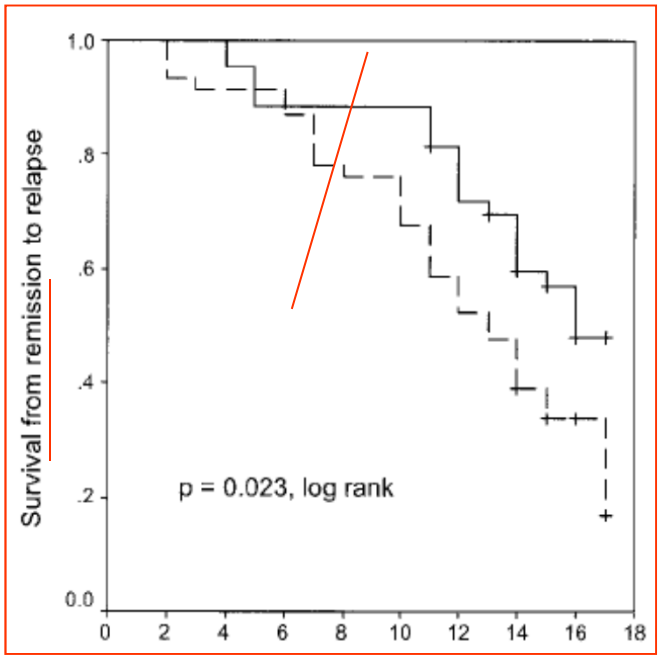
Remission at 6 mo
MTX 89.8%
CYC 93.5% (P=0.04)

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)

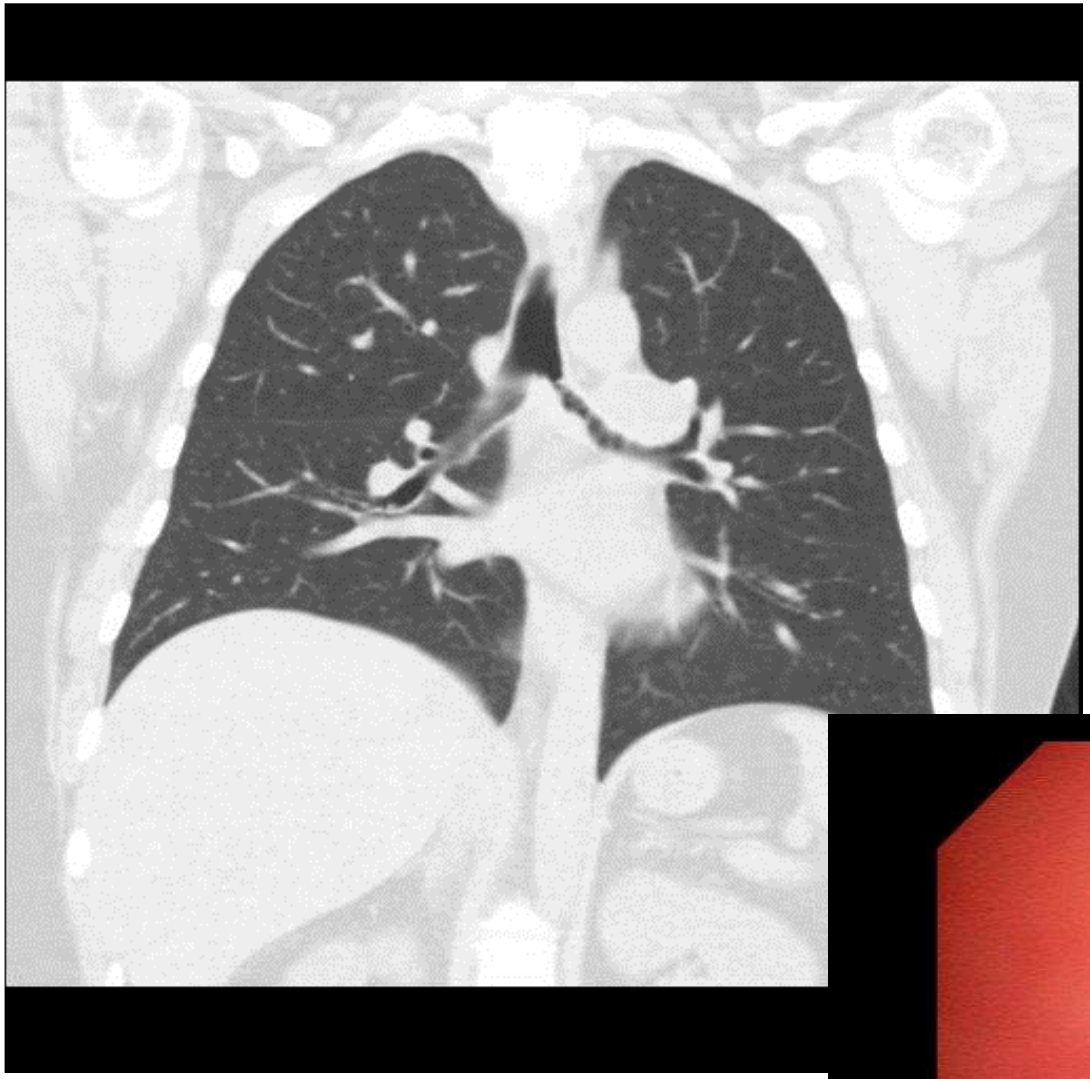


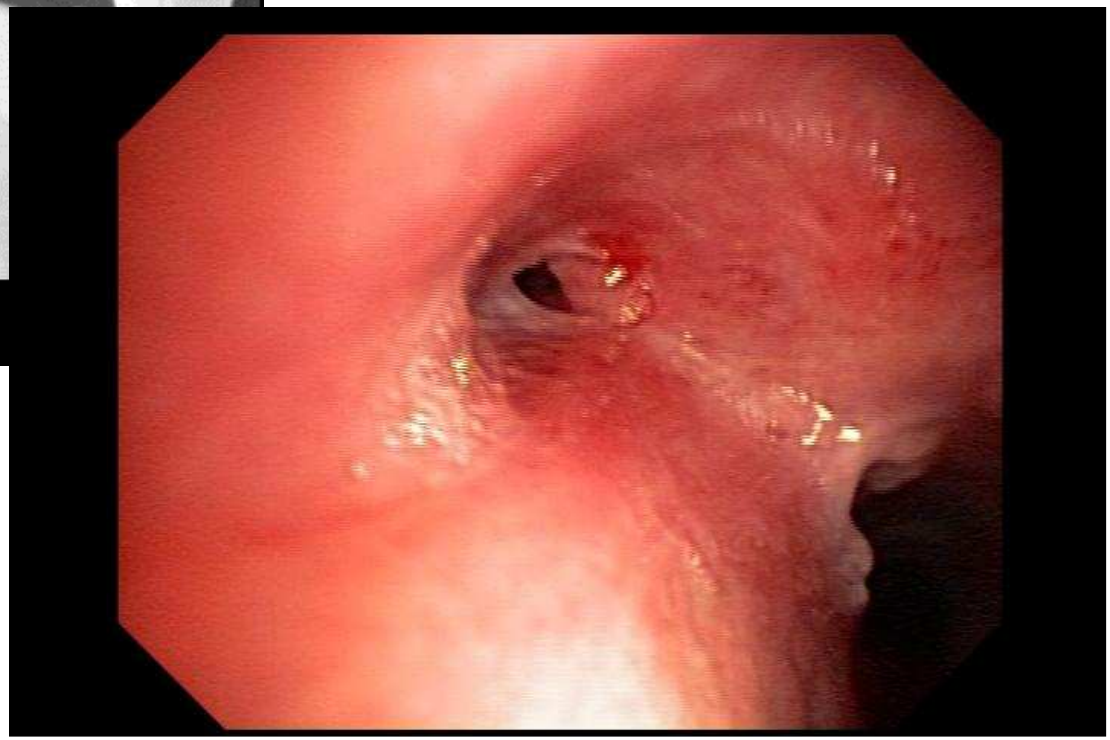


de Groot et al. *Arthritis Rheum* 2005;52:2461–9

Izeult, 32 years-old

- Methotrexate + Prednisone until 2004
- 2005: sinusitis, recurrent lacrimal duct obstruction then voice hoarseness & **stridor**…

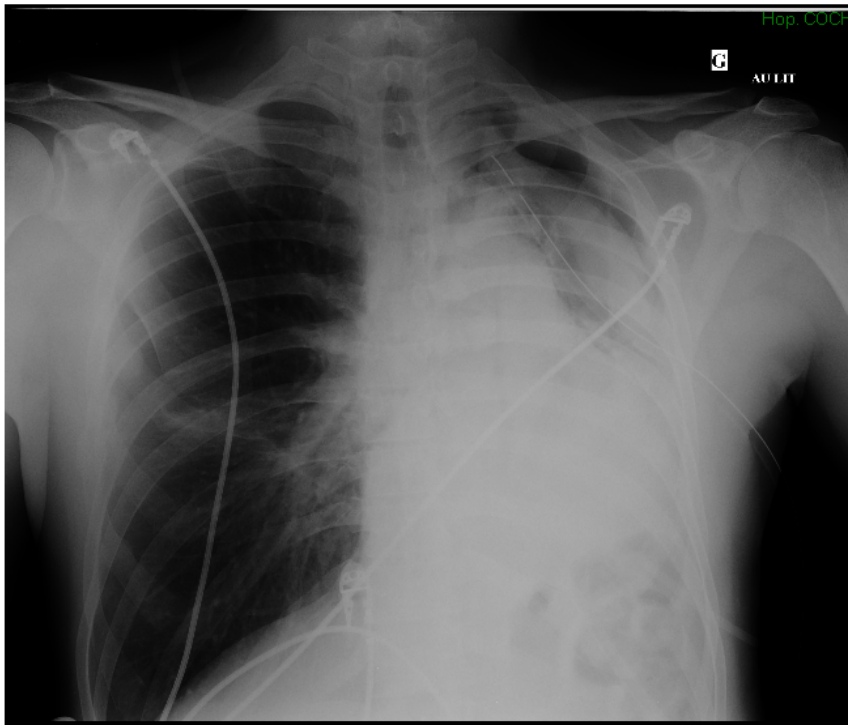


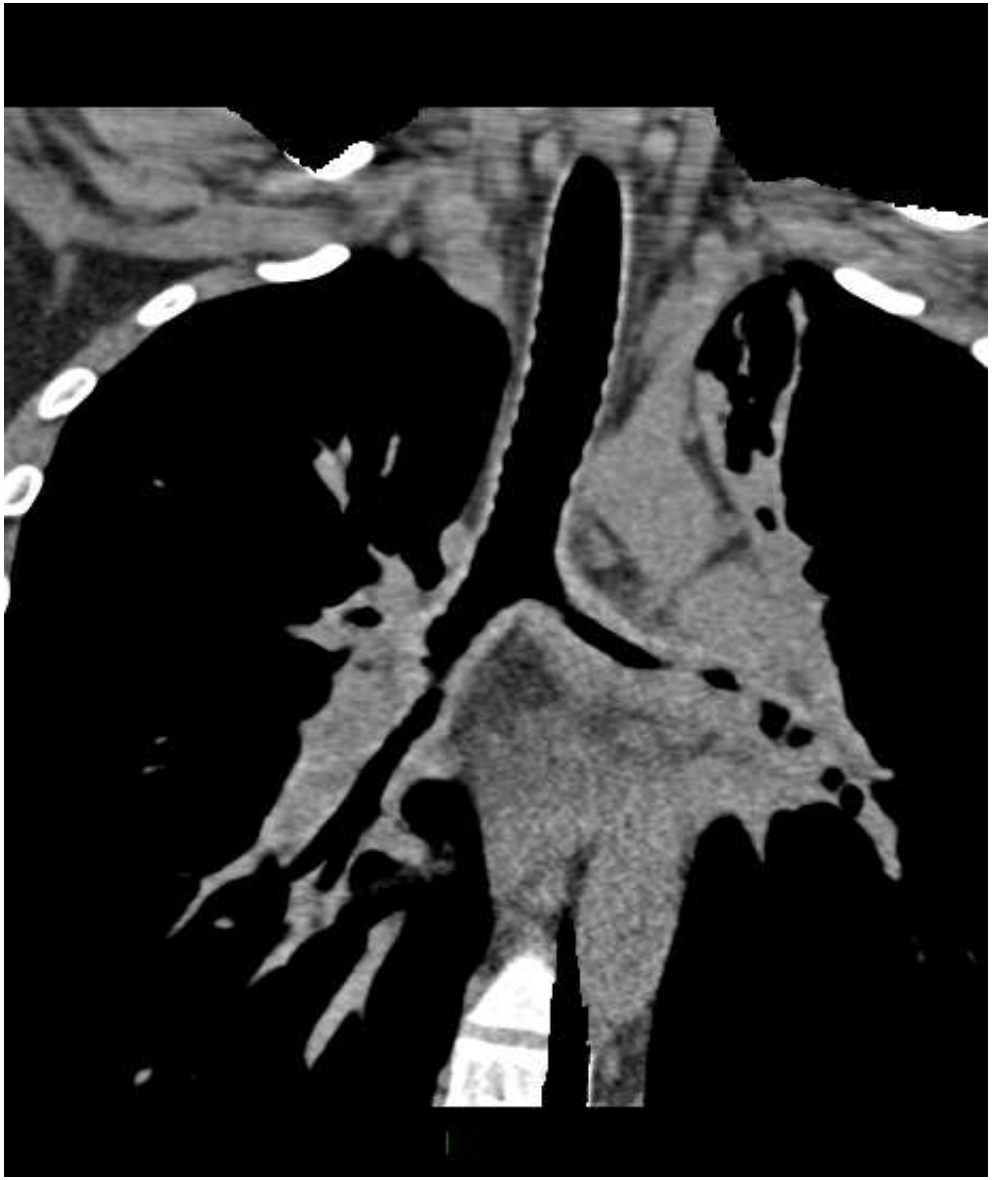


Bronchial stenoses in GPA

- 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

Hervier et al. Rev Med Interne 2006;27:453–457



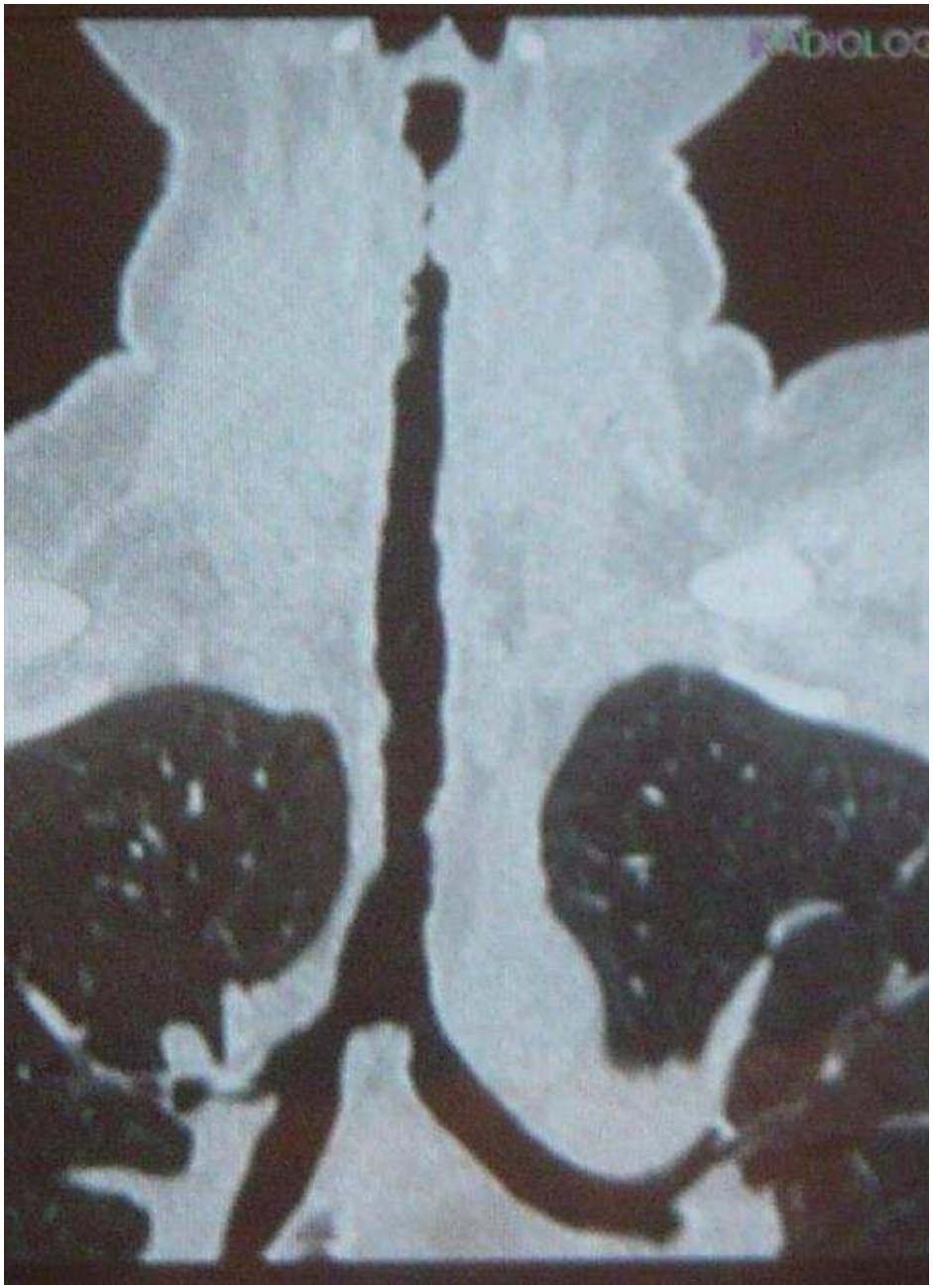


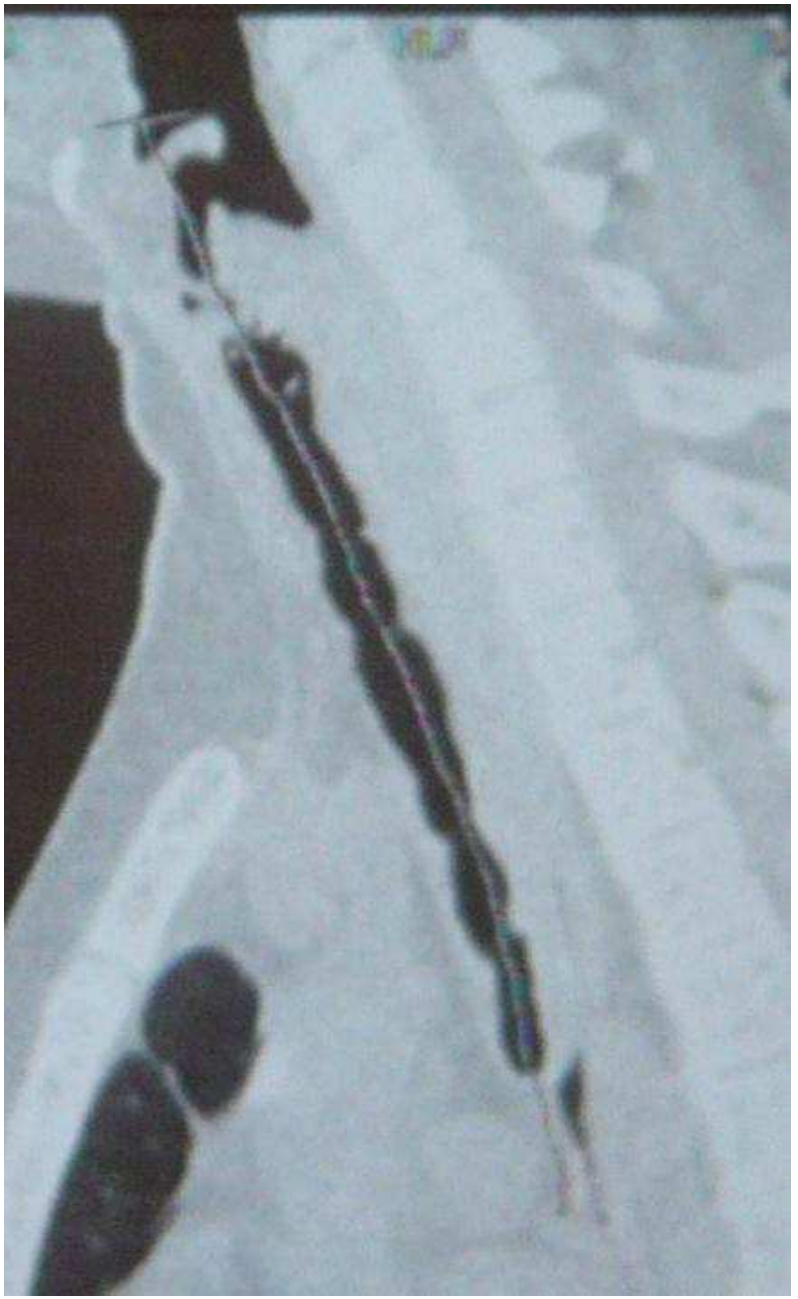

007 (Adulte)
Spin: 1
Tilt: -8

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**

Hervier et al. Rev Med Interne 2006;27:453–457





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)!!!

*Eliachar et al, Cleve Clin J Med 69 Supp.2:149-51
Lebovics et al, Laryngoscope 1992; 102:1341-5
Fowler et al. (Cleveland) ACR 2012, Chicago #1531

Cabral et . Arthritis Rheum 2009;60:3413–34
Langford et al, Arthritis Rheum 1996; 39:1754-60
Eustaqio et al. Arch Otol Head N Surg 2011;137:480-5

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)**

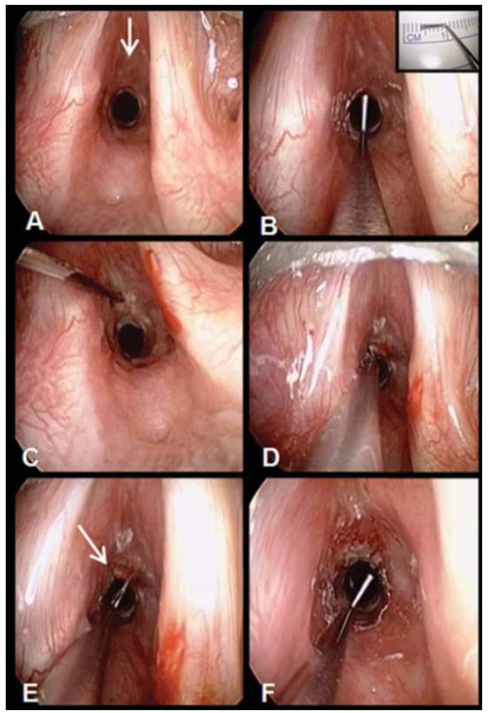
Hervier et al. Rev Med Interne 2006;27:453–457

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)

*Eliachar et al, Cleve Clin J Med 69 Supp.2:149-51
Lebovics et al, Laryngoscope 1992; 102:1341-5
Langford et al, Arthritis Rheum 1996; 39:1754-60
Wolter et al. Laryngoscope. 2010 Dec;120(12):2452-5

Systemic treatment

Corticosteroids….

+ ???

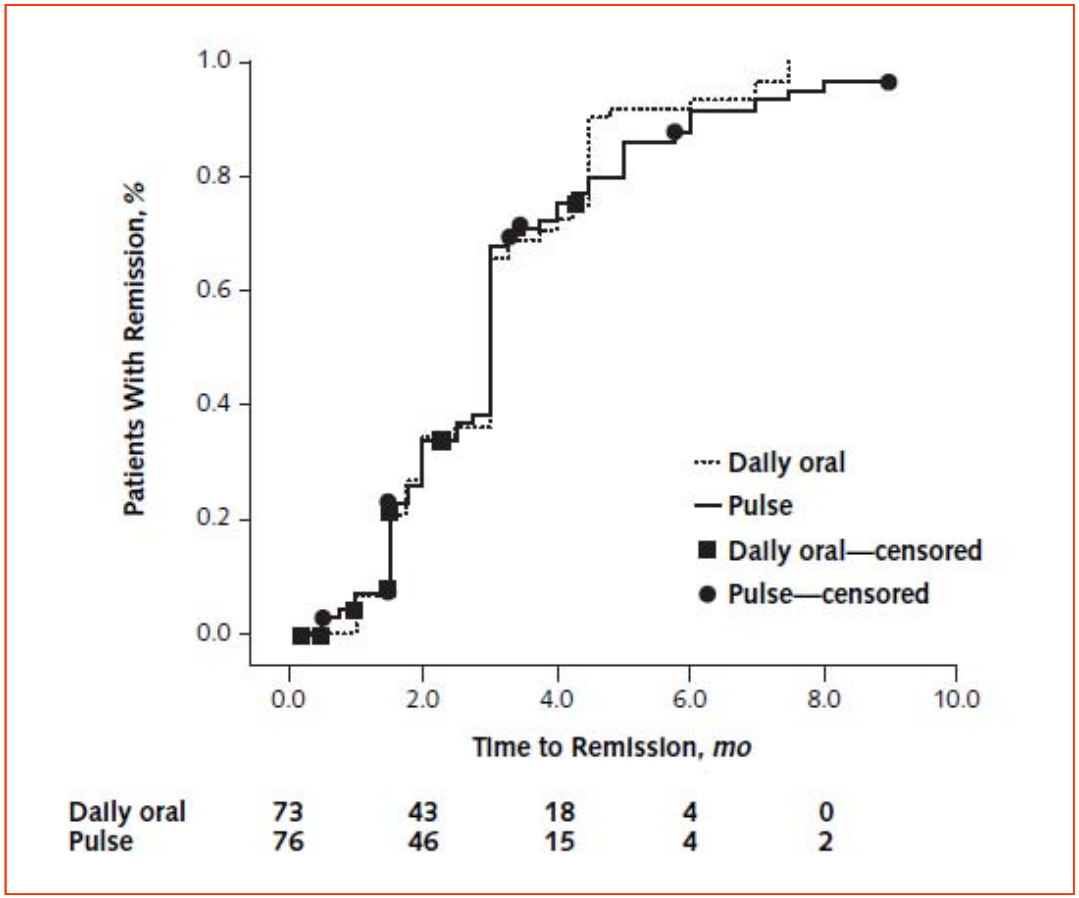
CYCLOPS

- Open label RCT
- 149 AASV (40% GPA)
- No Iº hypothesis
- Pulse (IV or oral) vs continuous oral CYC
- Remission <u>at 9 mo</u>

Pulse 88.1%

Continuous 87.7%

- IV pulse = lower rate of leukopenia HR 0.41 [CI, 0.23 to 0.71]

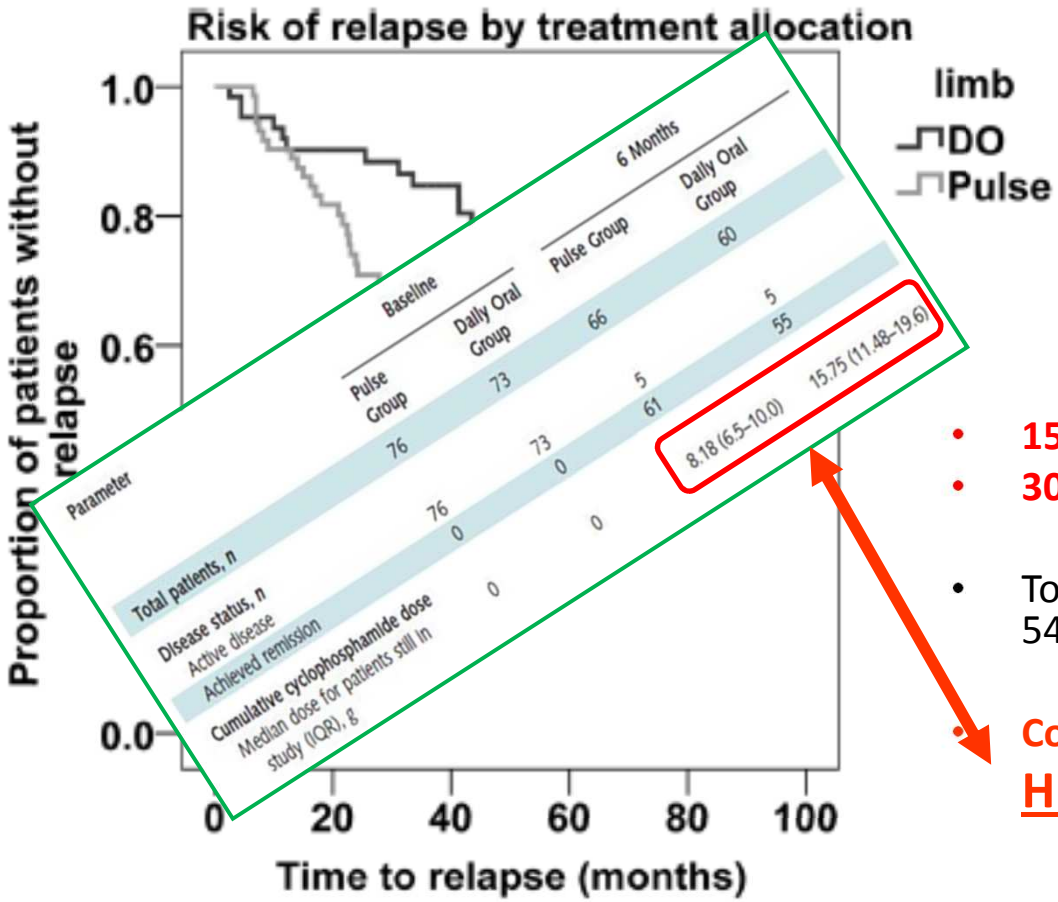


- <u>At 18 mo:</u>

14.5% relapsed

(18.8% IV vs. 9.4% PO)

de Groot et al, *Ann Intern Med* 2009;150:670-680.



Time (months)	0	20	40	60	80
DO (n)	72	55	46	26	2
Pulse (n)	76	64	54	24	3

Figure 2. Relapse-free survival in the two treatment arms. Using Kaplan–Meier survival analysis, there was a significantly increased risk of relapse during follow-up in patients randomised to pulse cyclophsophamide rather than daily oral (DO) treatment (p=0.029).

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**

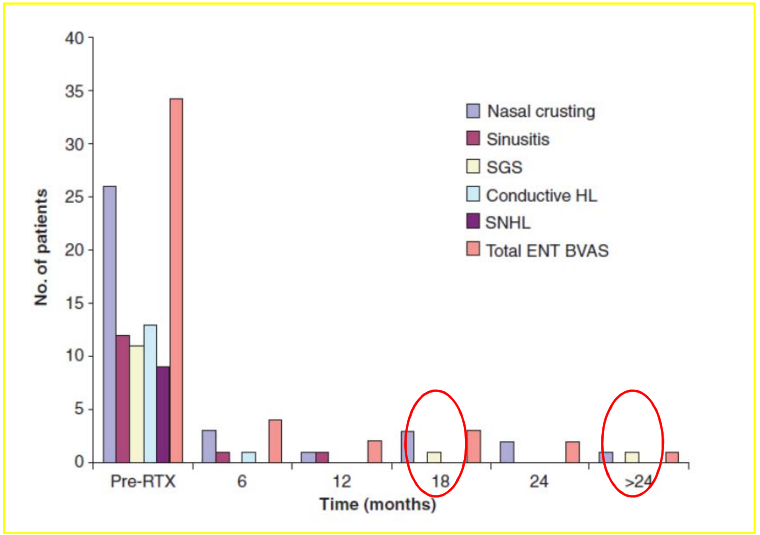
HR=0.50, 95% (CI, 0.26-0.93); p=0.029

Harper et al. Ann Rheum Dis. 2011 Nov 29. [Epub ahead of print]

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

- Del Pero et al. Clin. Otolaryngol. 2009, 34, 328–335
  - 11 patients with SGS
  - “Vasculitis affecting the sub-glottis […] responded to treatment without recurrence, but left permanent damage”



Rituximab in SGS

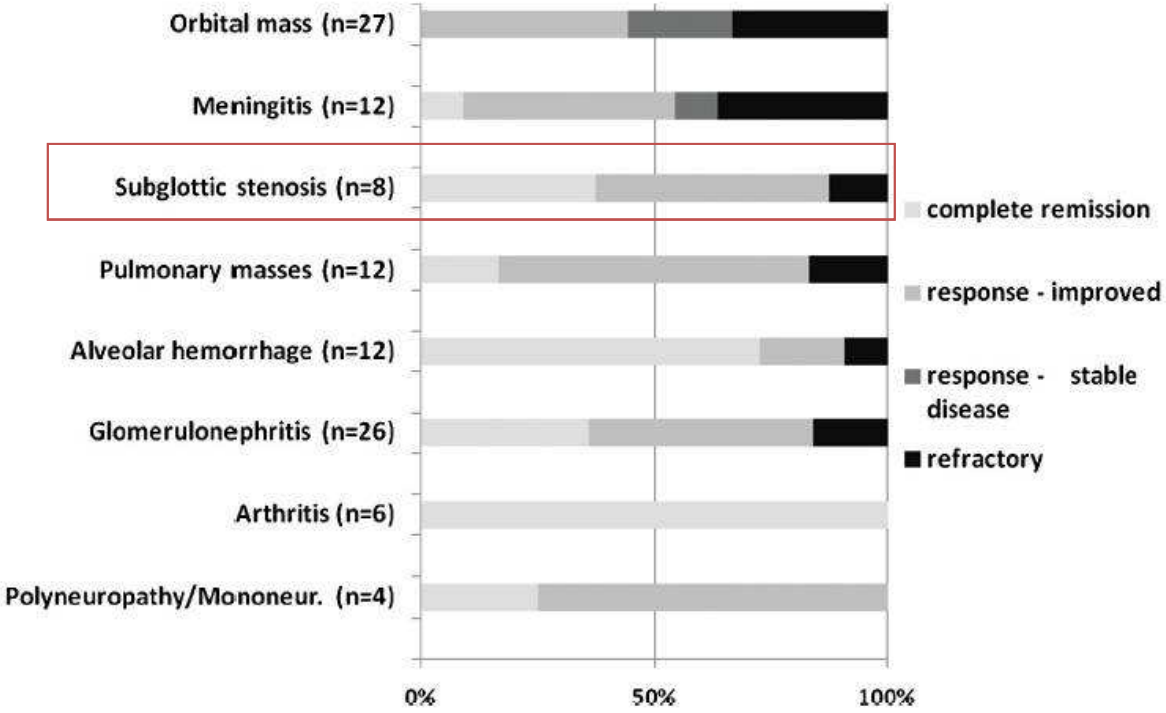


Figure 3 Efficacy of rituximab (RTX) by organ involvement given for the most frequent organ involvements (in at least four patients or more). For efficacy of RTX in organ involvements that were less common see online supplementary material.

Holle et al. Ann Rheum Dis. 2012 Mar;71(3):327-33

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

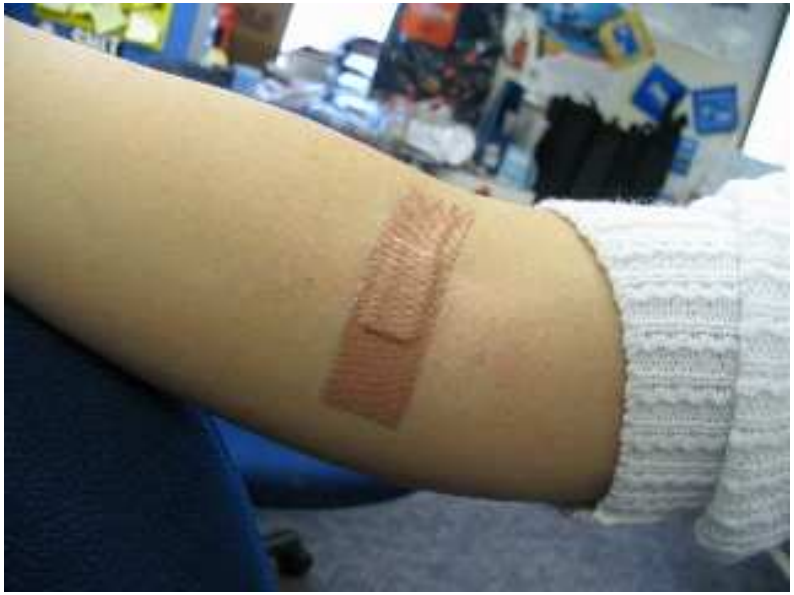
- **pmHx:**
  - Healthy
  - No exposures

Examination

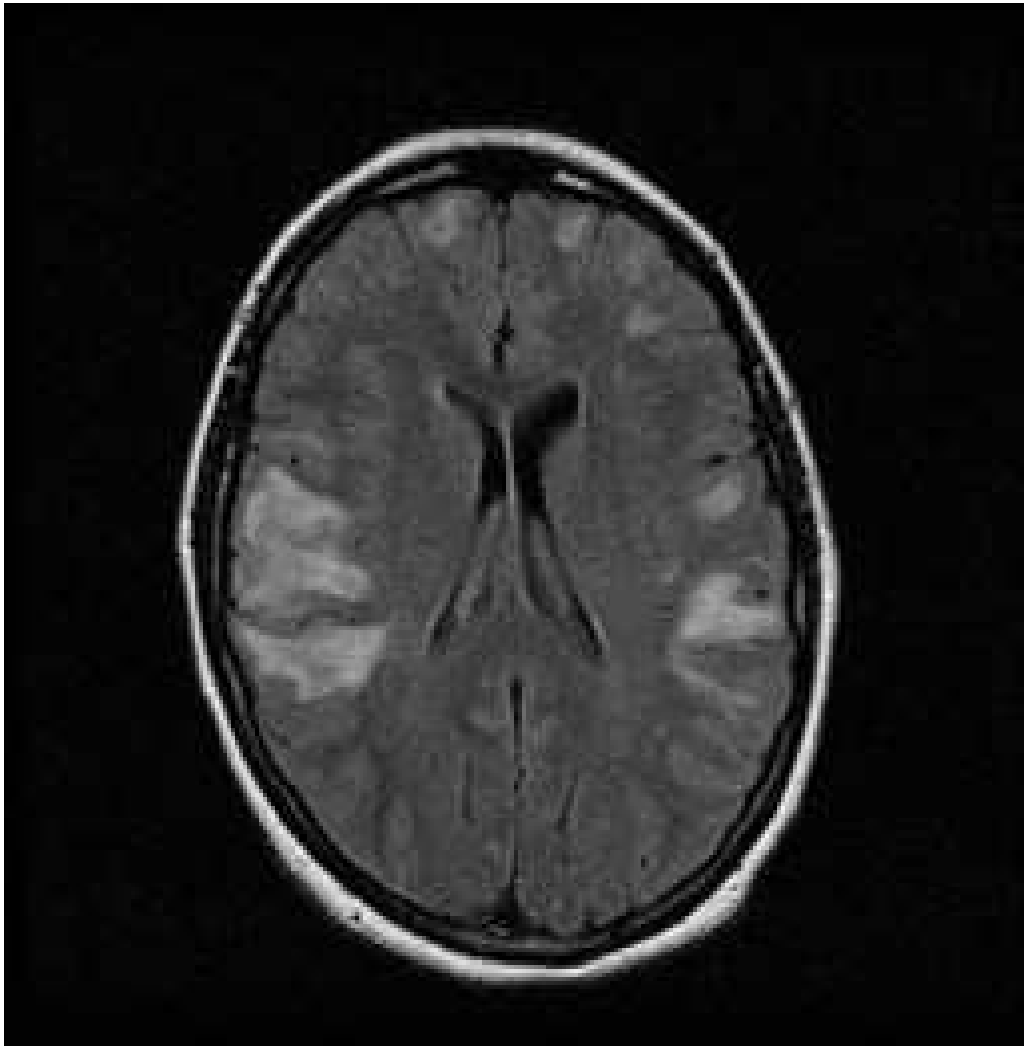
- **O/E**
  - Vital signs: tachycardia, Temp 38.0°C, normal blood pressure, unwell
  - General physical examination: normal
  - **Neurological examination:**
    - hyperreflexic, photophobic
    - severe headaches
    - Seizure status, continues bilateral seizures

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

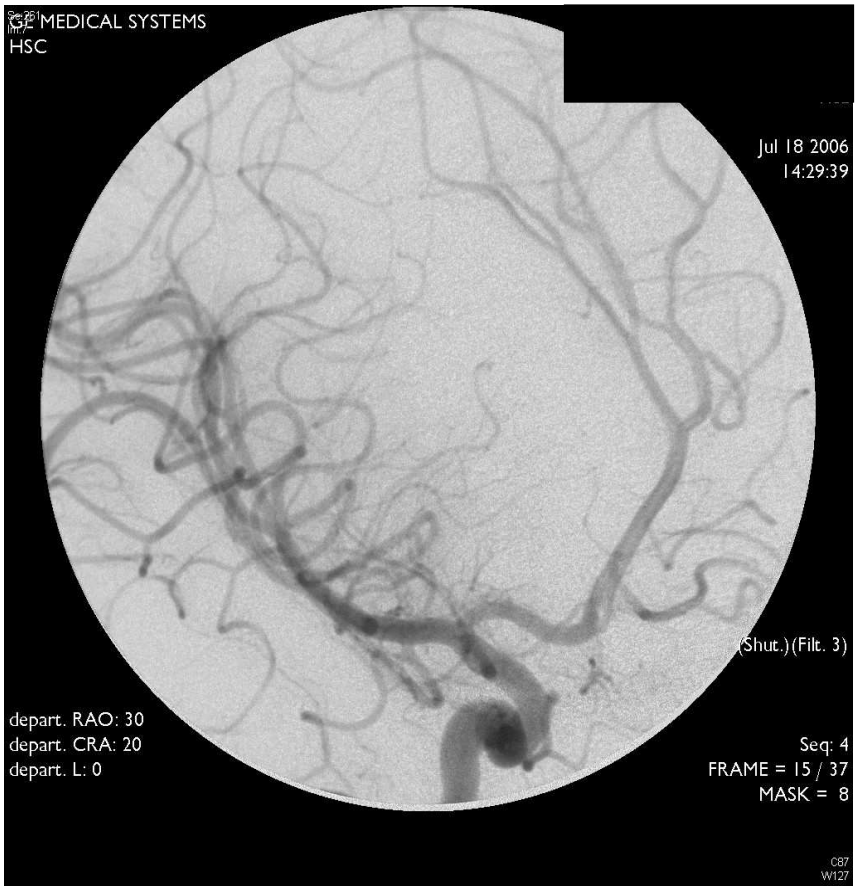


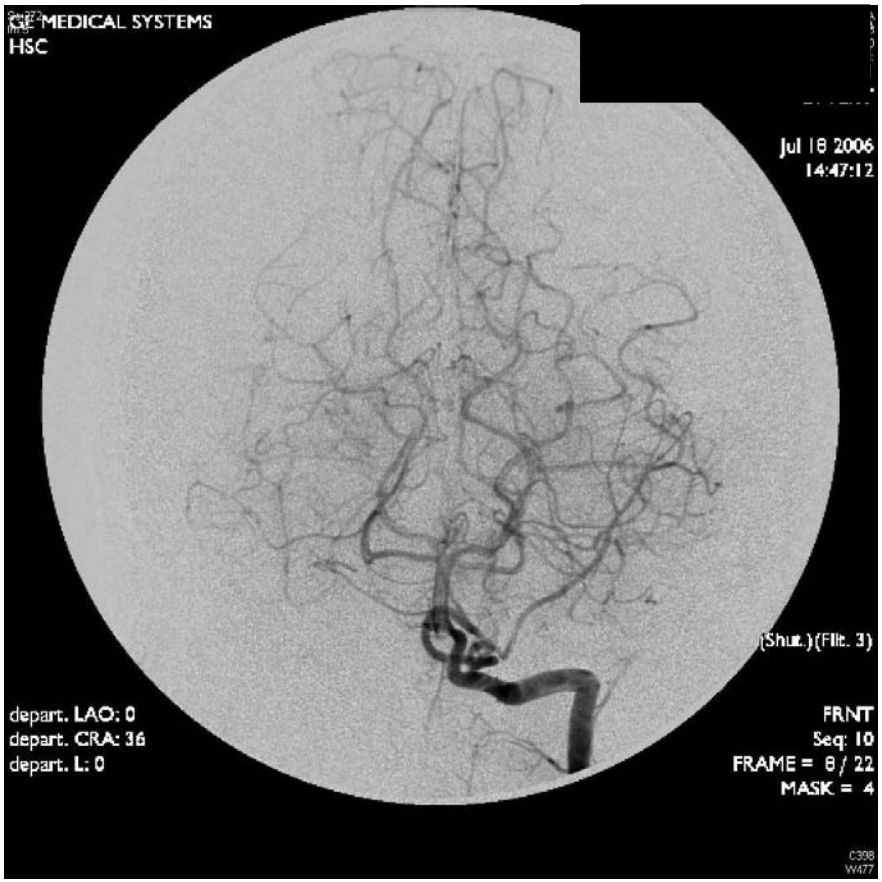
MRI



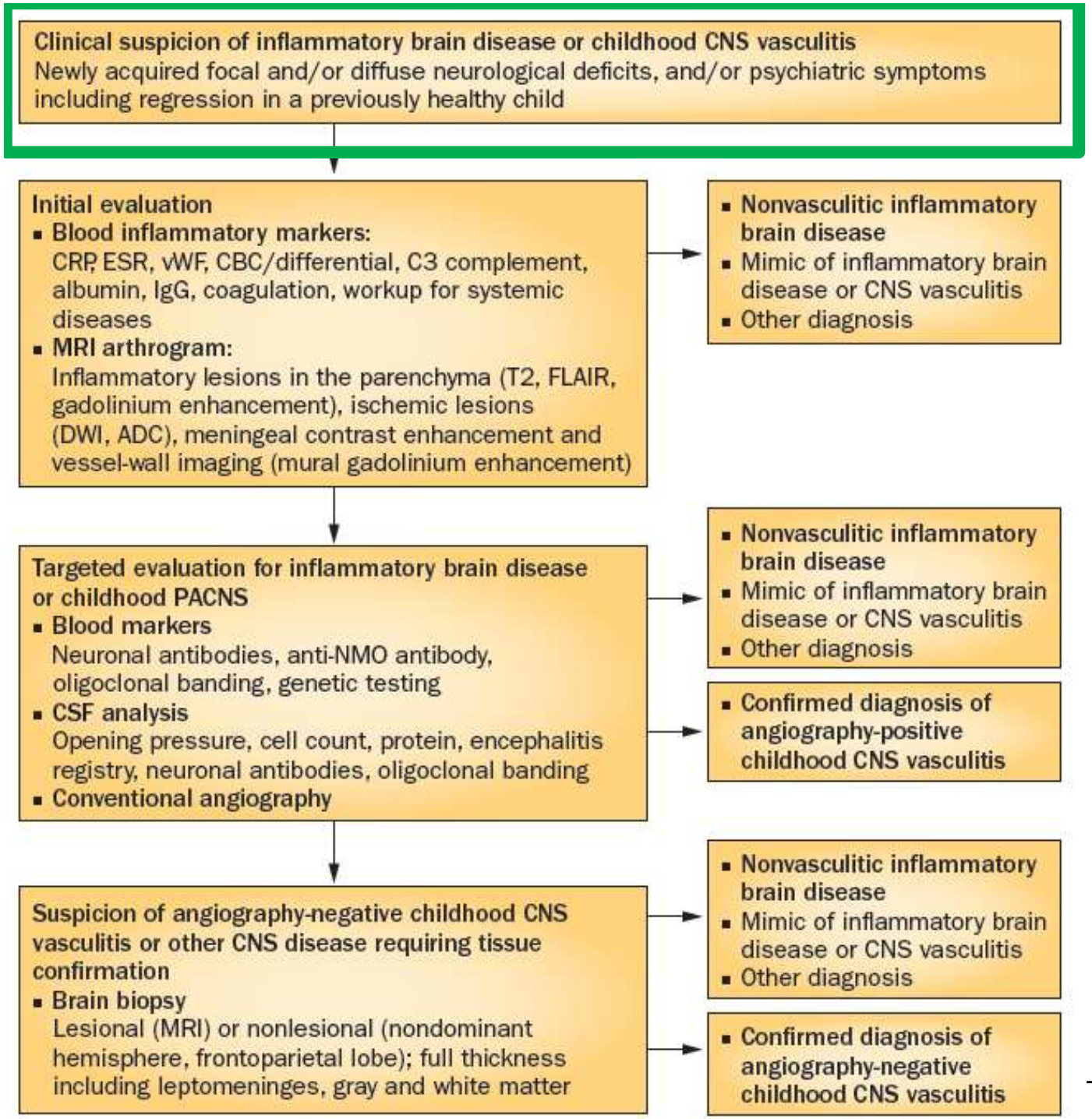
- White and grey matter lesions,
- Leptomeningeal contrast enhancement

MRA, Conventional Angiography

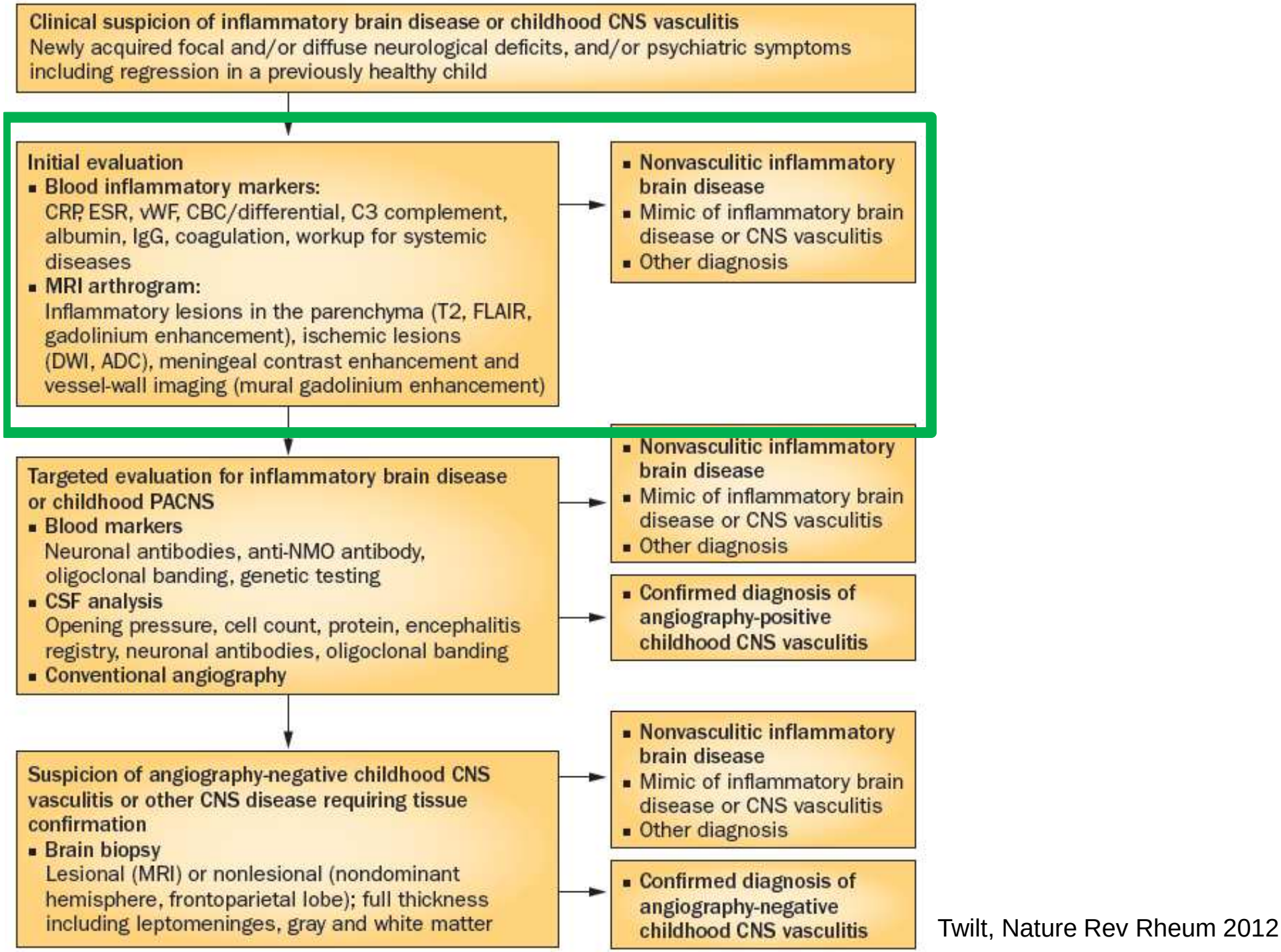




normal



Twilt, Nature Rev Rheum 2012



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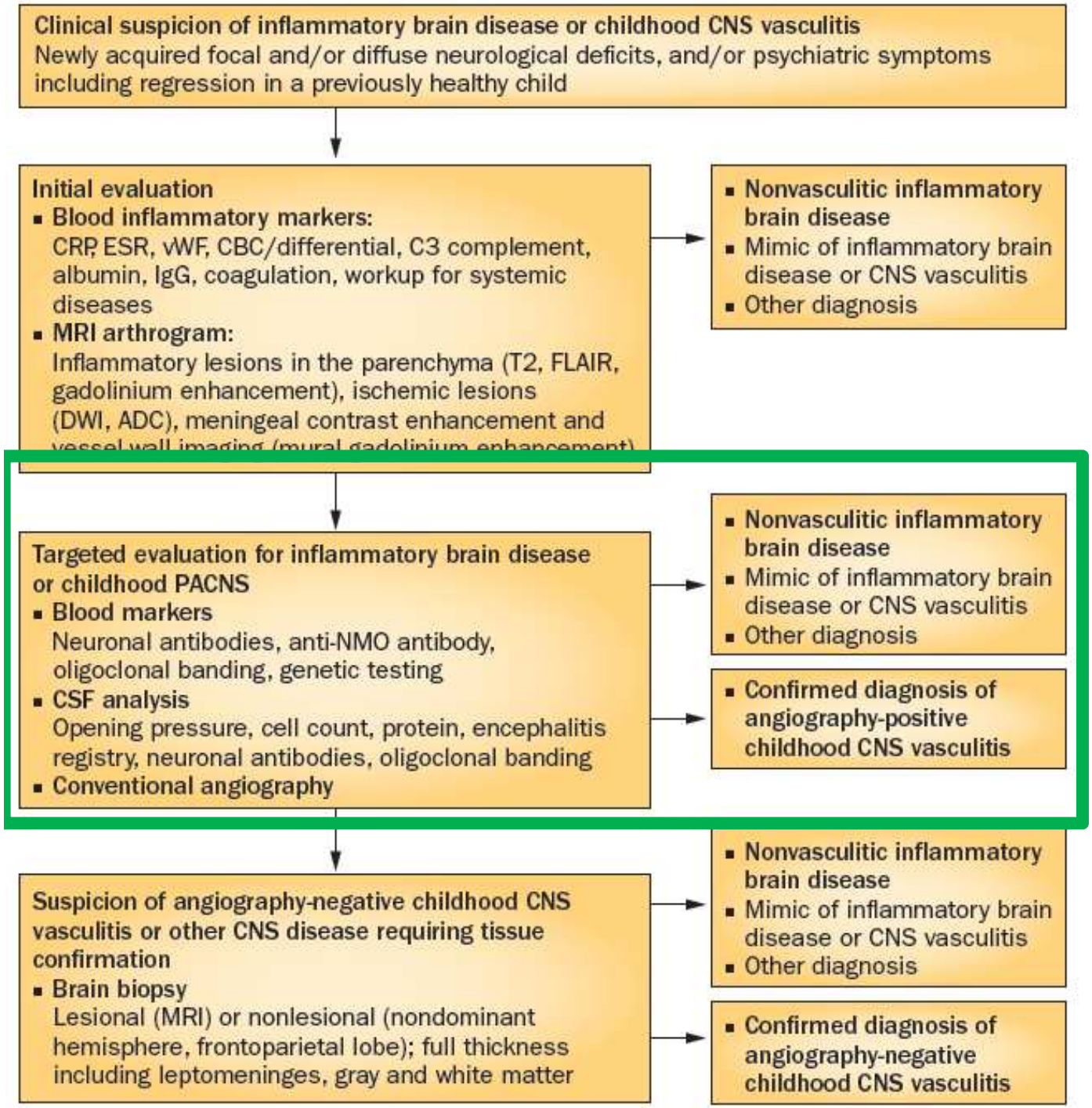

Twilt, Nature Rev Rheum 2012

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

Cellucci 2010, Current Opinion Rheumatology

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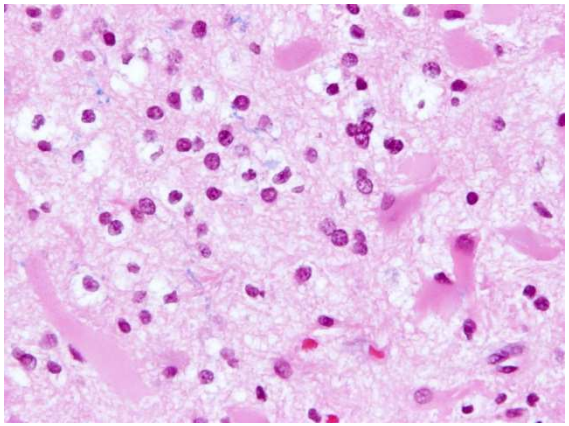
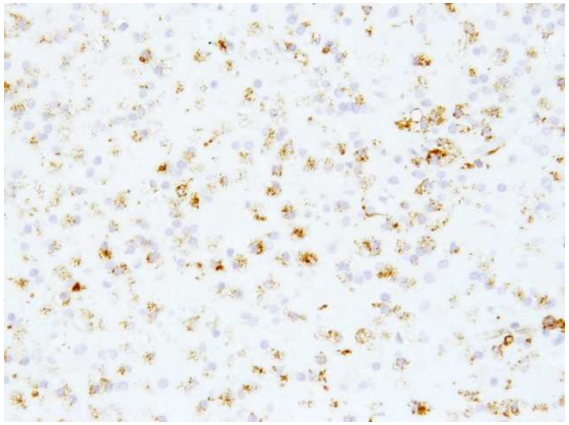
Cellucci 2010, Current Opinion Rheumatology

Demyelinating diseases



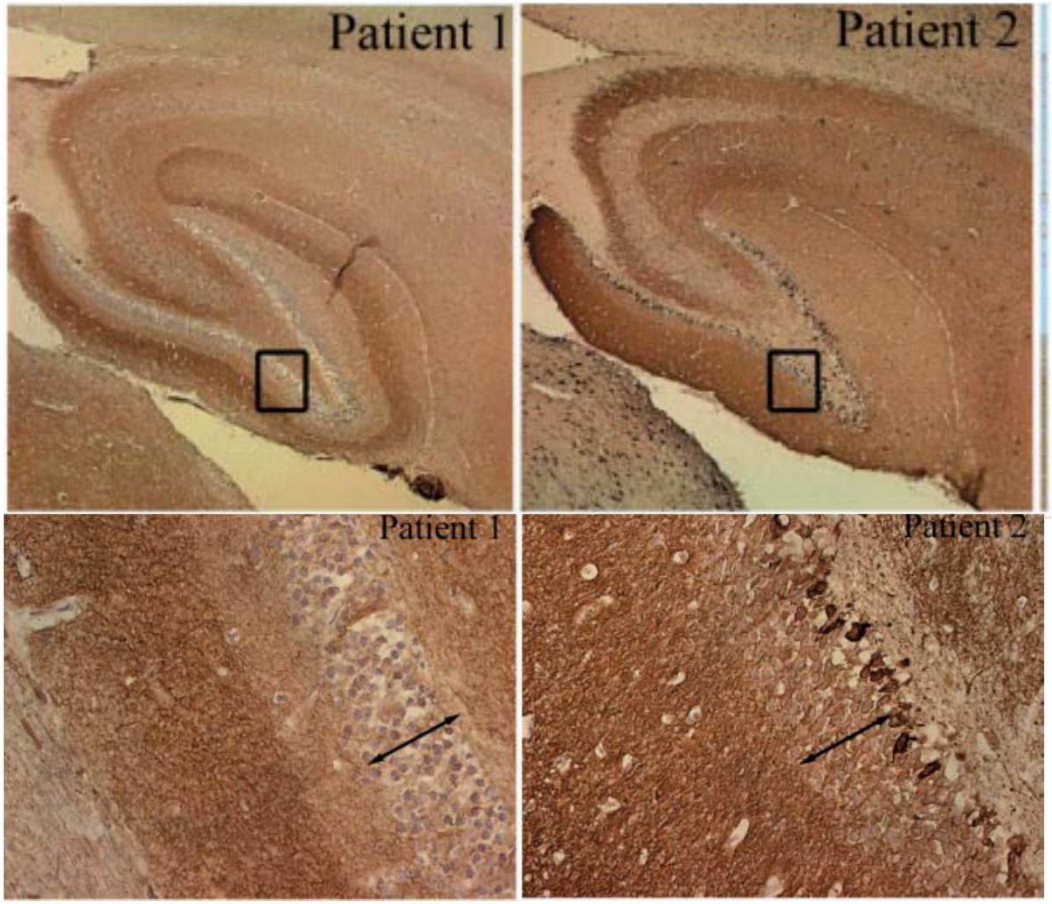
- Inflammation targets white matter and causes demyelinating plaques
  - Myelin filled macrophages



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

Courtesy Cynthia Hawkins, July 2011

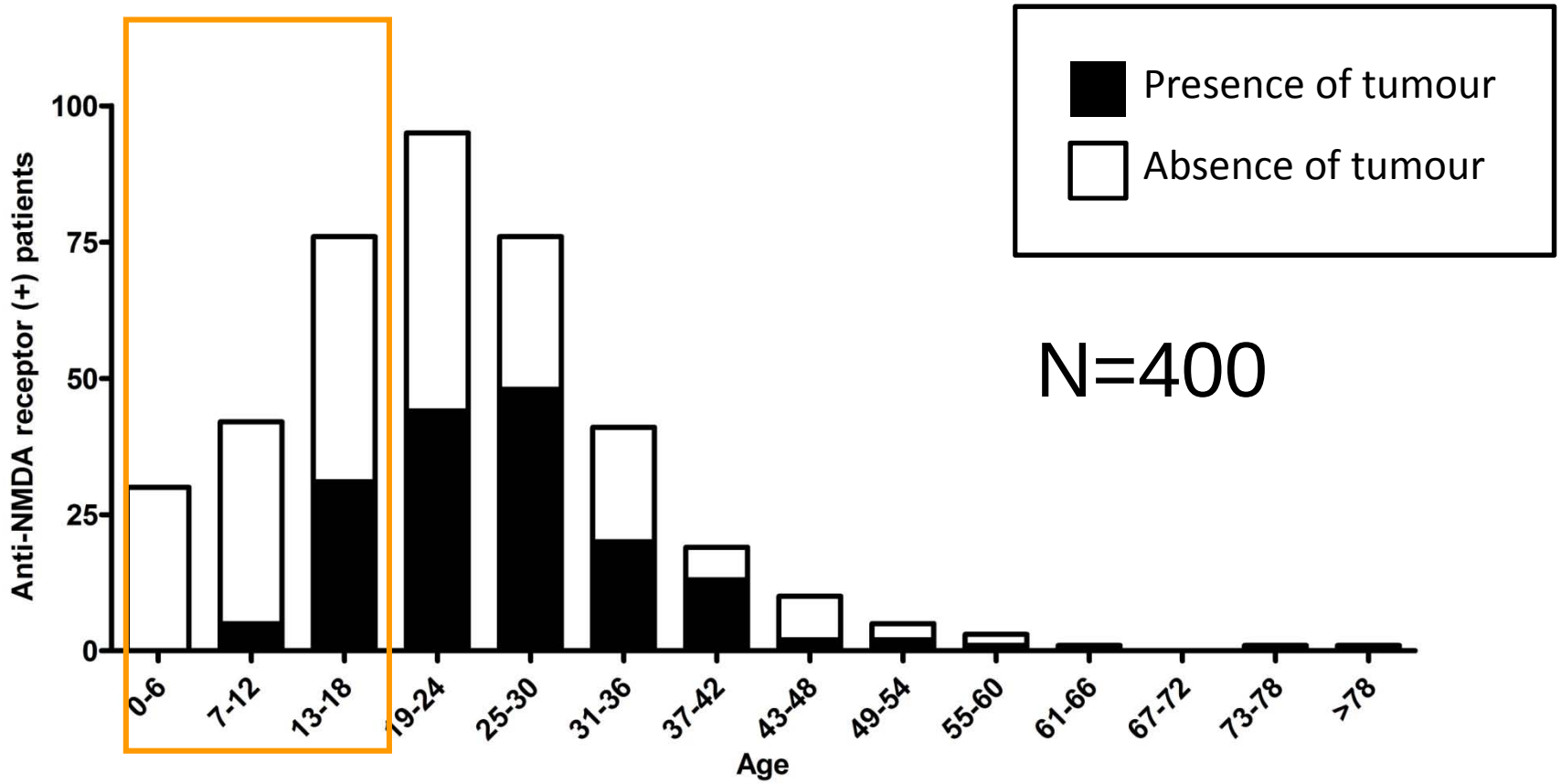
Neuronal antibody associated IBrainD



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

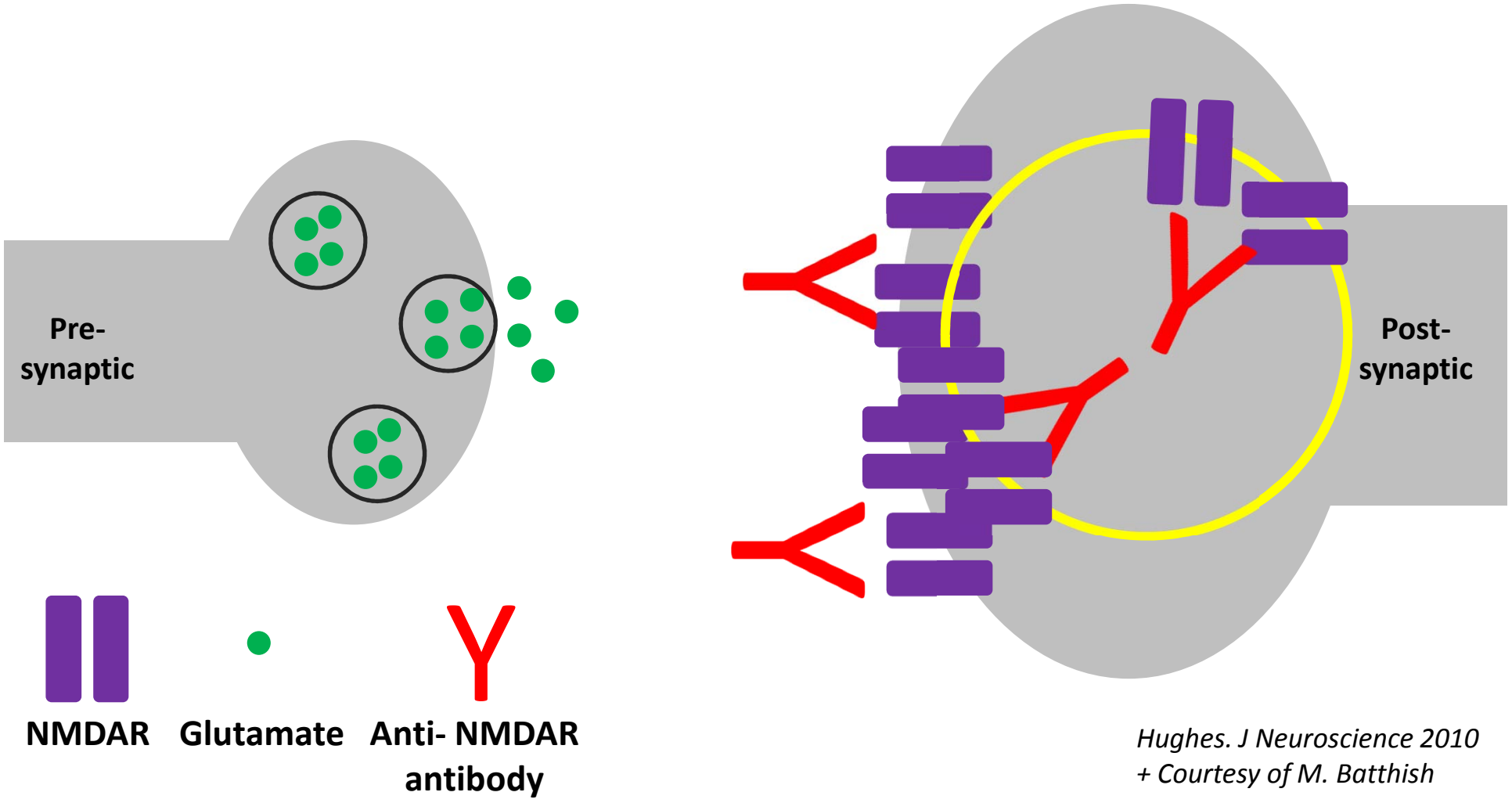
Dalmau 2005

Anti-NMDAR Encephalitis



Dalmau et al. Lancet Neurology 2010

Antibodies cross-link and cause internalization of NMDAR



Hughes. J Neuroscience 2010
+ Courtesy of M. Batthish

NMDA Receptor Encephalitis

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

Dalmau, 2008

Neuromyelitis optica NMO

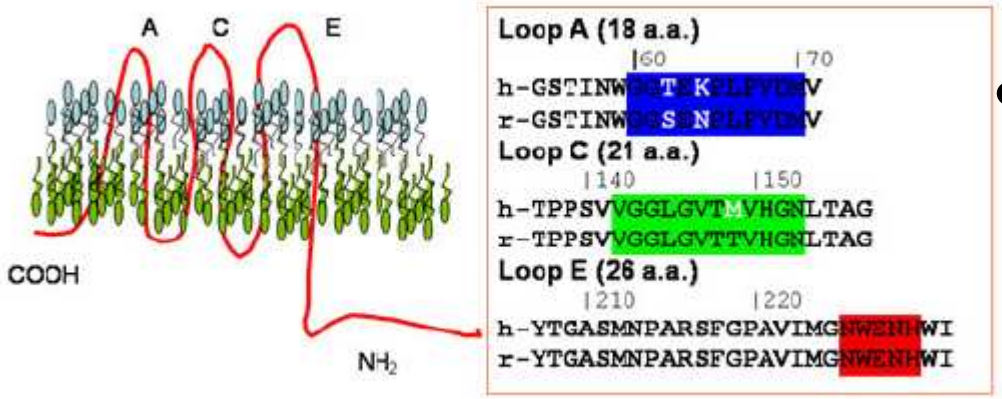
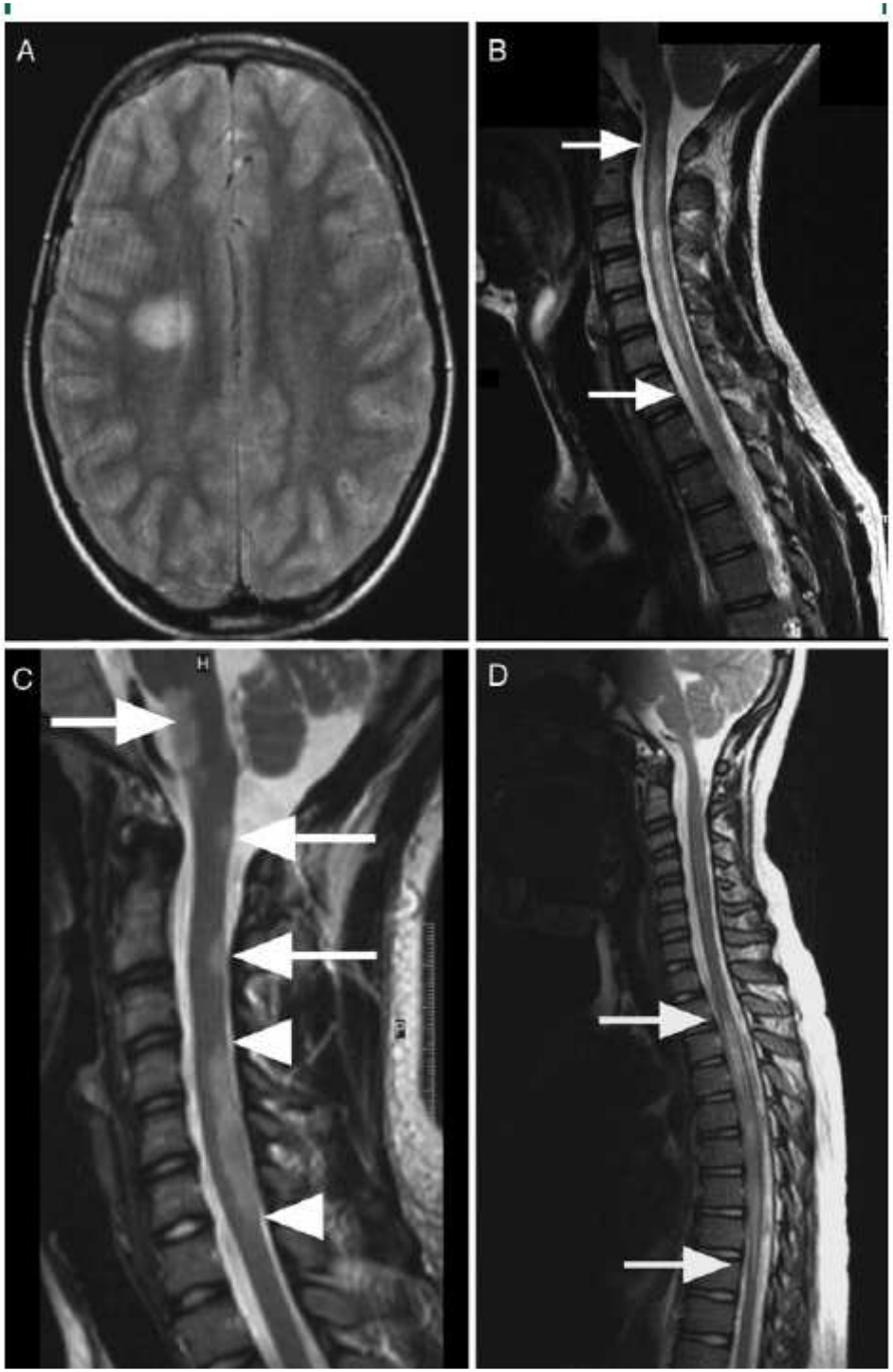


Figure 1
Aquaporin 4 is a type III water channel regulator with limited surface exposed residues. AQP4 has been

- Auto-antibodies against Aquaporin4
- CSF ± serum

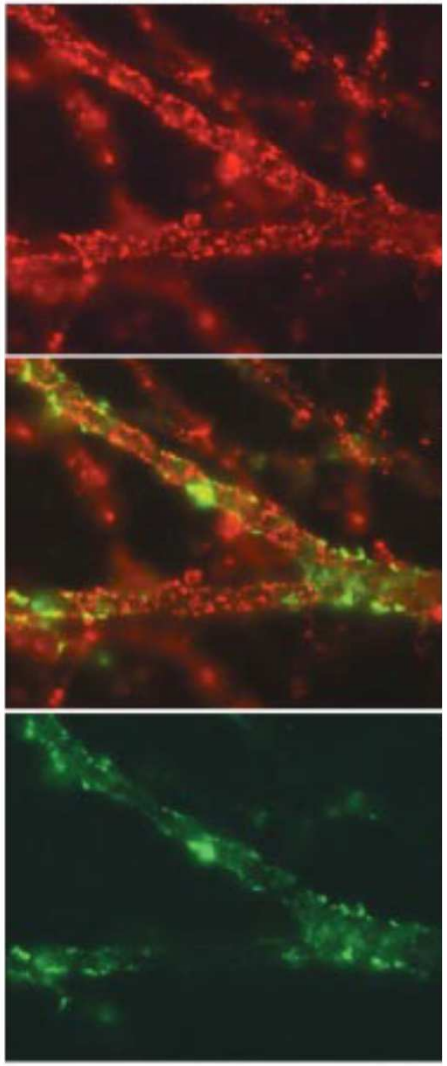
Graber, 2008



NMO

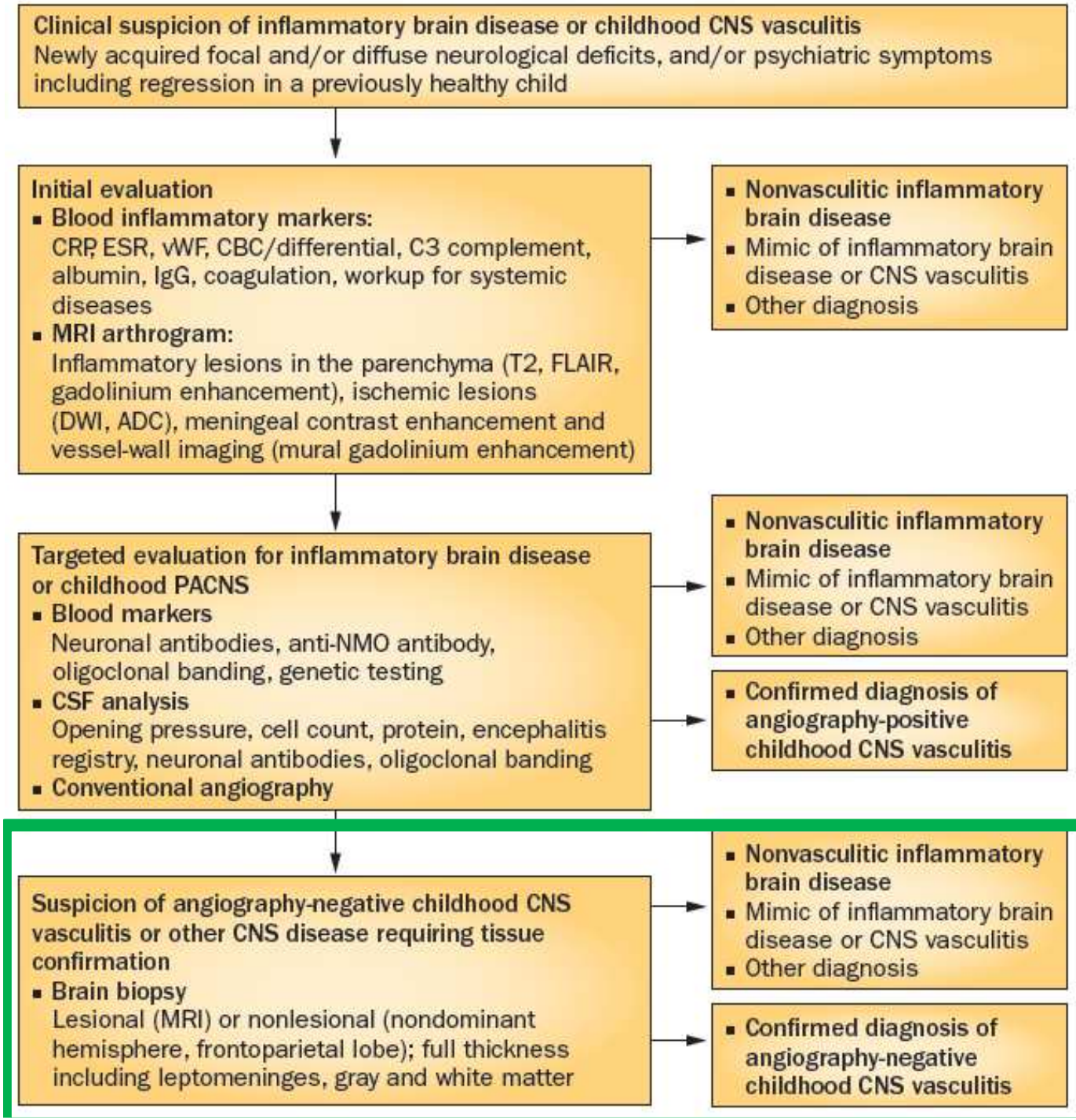
Banwell, 2008

Limbic encephalitis



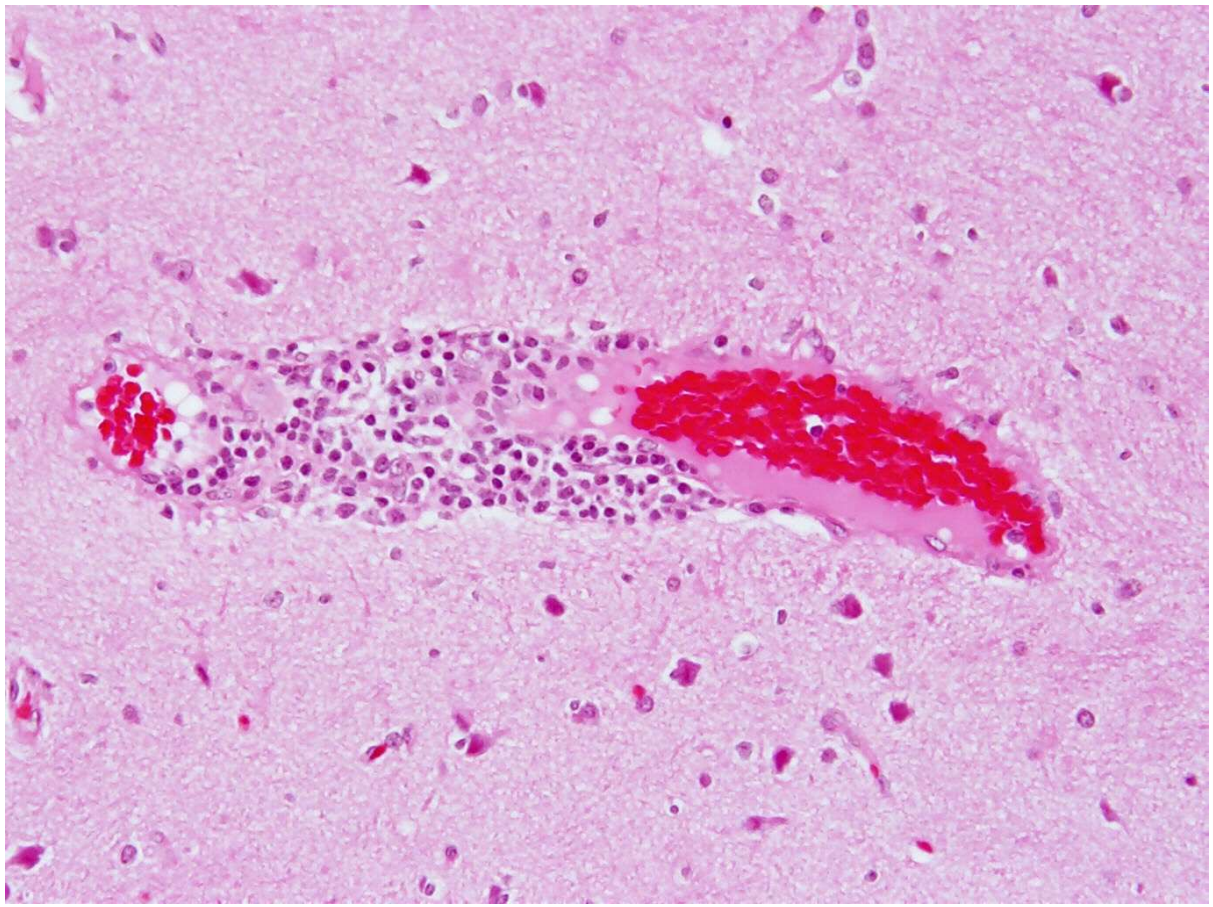
- **Paraneoplastic** antibodies
  - Hu, Ma
- Auto-antibodies against LGI
  - Secreted antigen associated with **Voltage-gated potassium channels**
  - AMP: anchor protein for LGI
  - AMP-binding protein

Dalmau 2005, 2010
Haberlandt, Bien 2010



Twilt, Nature Rev Rheum 2012

Brain biopsy



Lymphocytic small vessel vasculitis

Diagnosis:

Primary CNS Vasculitis of childhood

Angiography-negative,

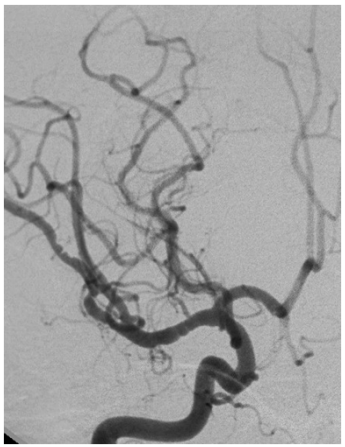
small vessel SVcPACNS

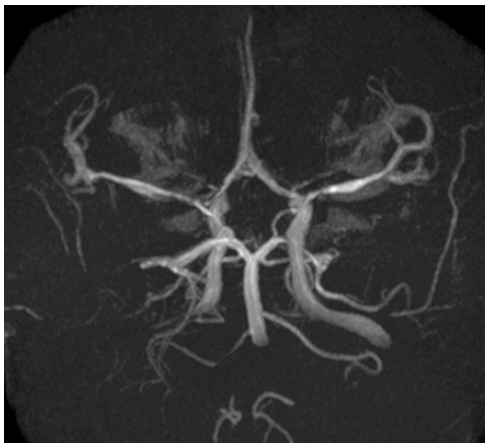
Modified **Calabrese criteria: cPACNS**

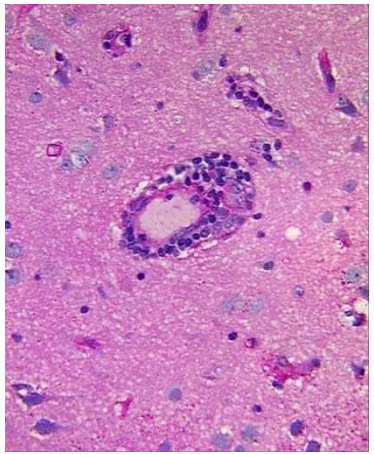
- **Clinical evidence** of a newly acquired focal and/or diffuse neurological deficit or psychiatric syndrome in a **patient ≤18 years** of age **plus**
- **angiography** and/or **brain biopsy** evidence of CNS vasculitis
- in the **absence** of a significant underlying condition known to cause or mimic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

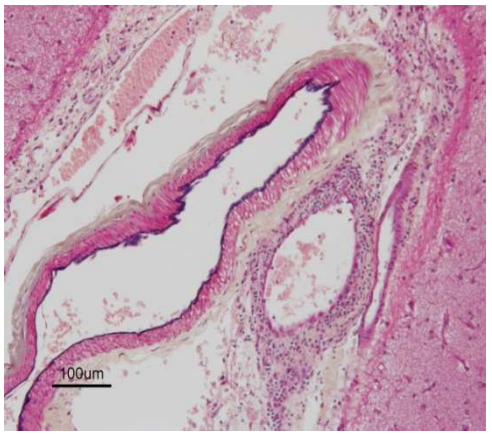
Calabrese, 1988
Benseler 2005, 2006

Primary CNS Vasculitis of Childhood









Angiography-positive cPACNS

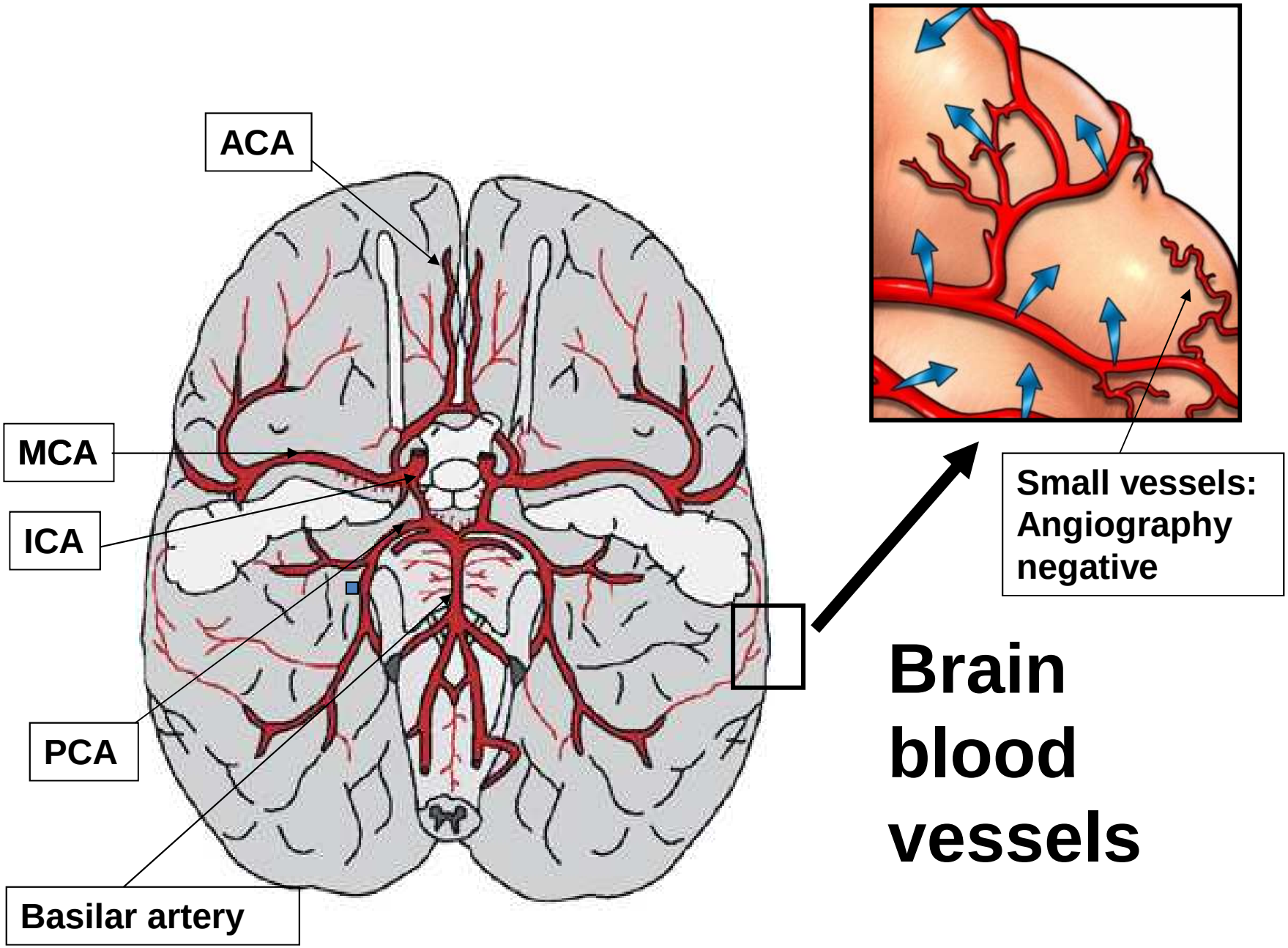
Large vessel disease

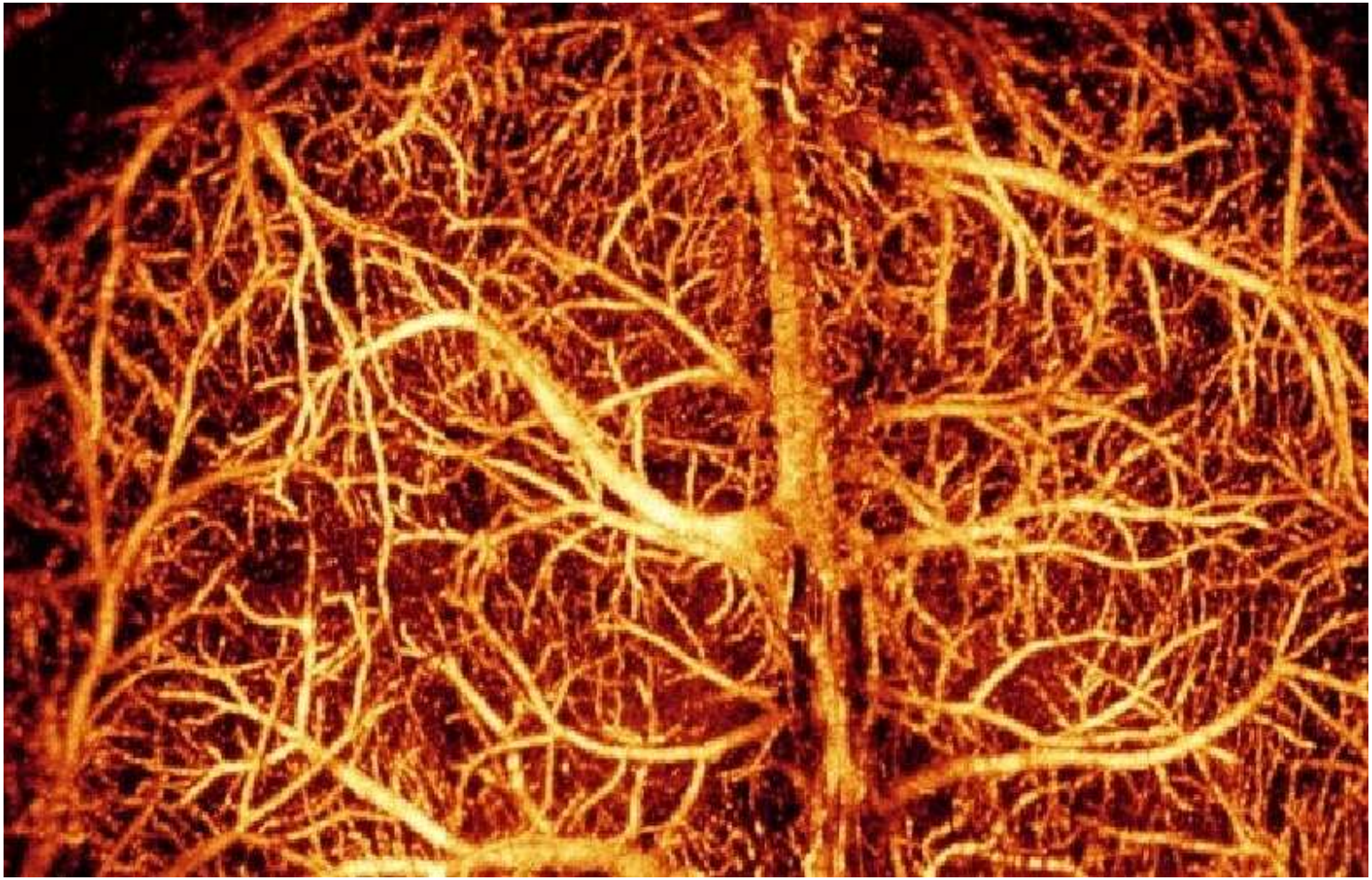
Angiography-negative cPACNS

Small vessel disease

Benseler 2005, 2005

Elbers, 2011


ACA
MCA
ICA
PCA
Basilar artery
Small vessels: Angiography negative
Brain blood vessels



CNS vessels

SVcPACNS protocol

SickKids

BRAINWORKS

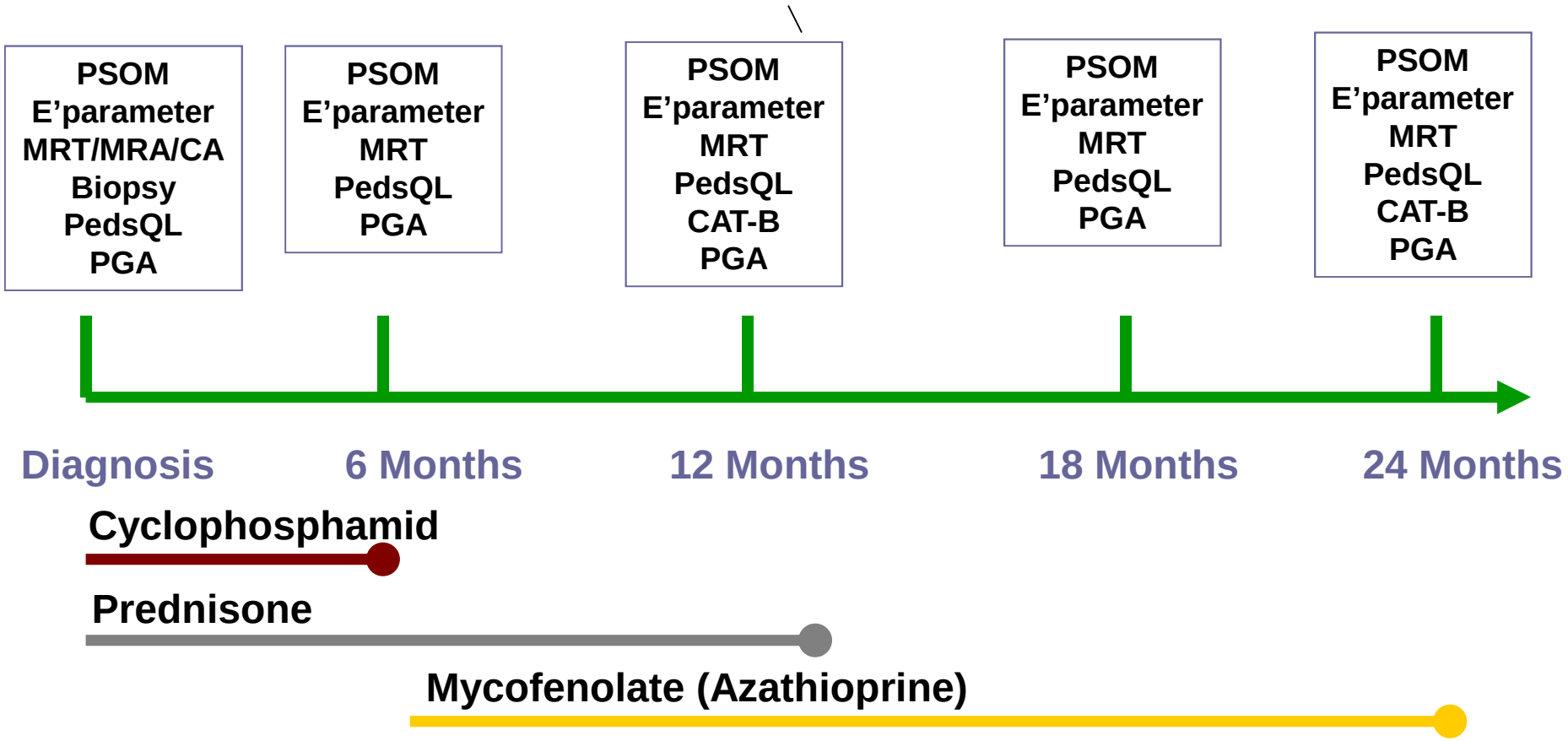
The International Childhood
CNS Vasculitis Outcome Study

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 x18 month** MMF 800-1200mg/m^2/d (Azathioprine 2mg/kg/d max 150mg)

Hutchinson, 2010 *Lancet Neurology*

SVcPACNS treatment protocol



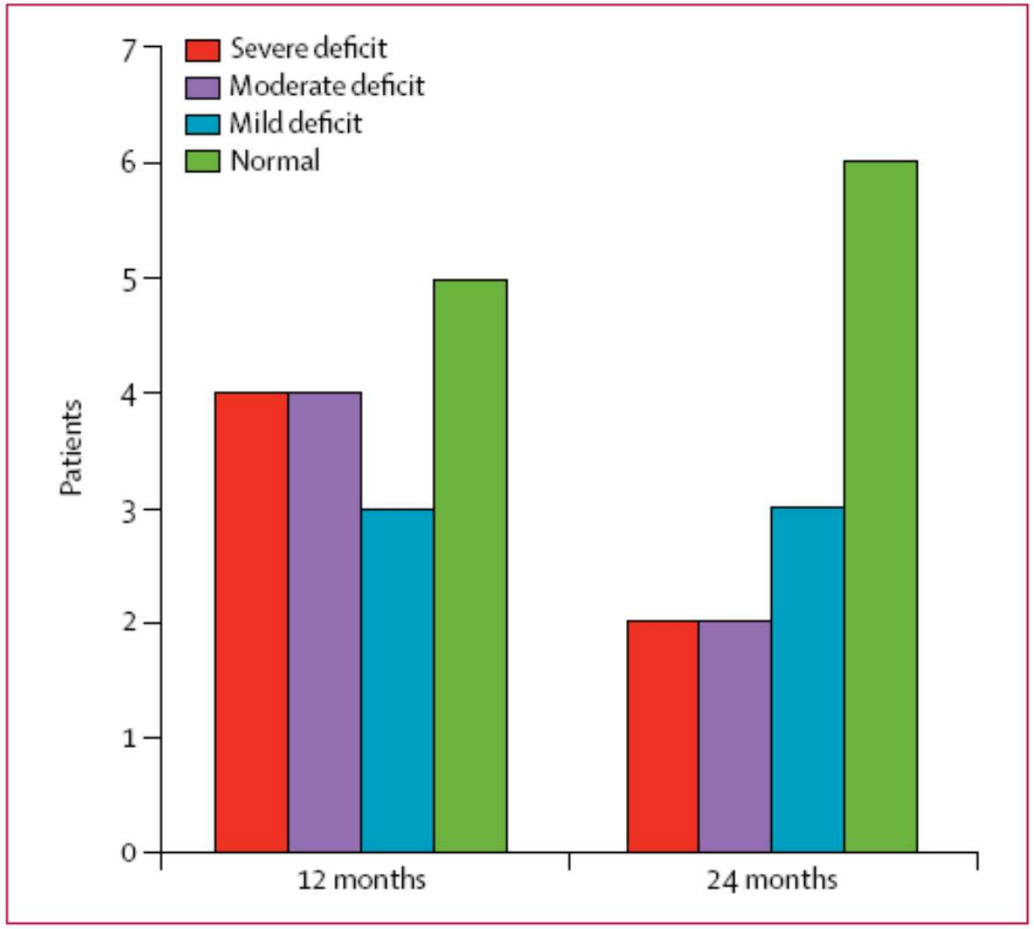


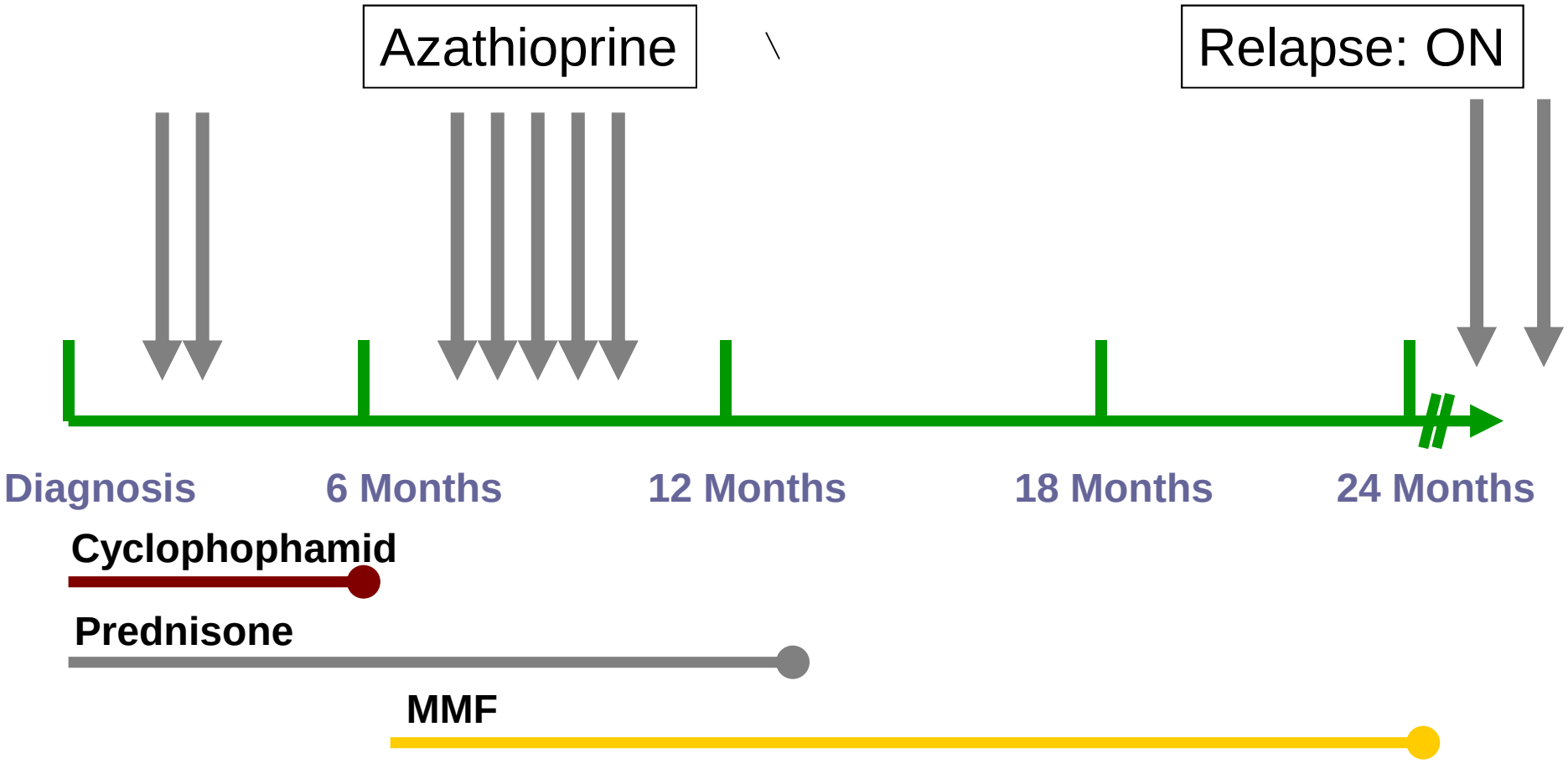
Figure 3: Neurological outcome in children with small vessel childhood primary angiitis of the CNS, as measured by the paediatric stroke outcome measure score

at 24 months

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

Hutchinson, 2010 Lancet Neurology

SVcPACNS Flares



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!


CANVASC


BRAINWORKS
The International Childhood
CNS Vasculitis Outcome Study


ARChiVe


CARRA