

CNS vasculitis of infectious origin



**Grenoble
ESCMID course
29 Oct 2014**

Marie Studahl, Department of Infectious
Diseases, Sahlgrenska University Hospital

Definition of CNS vasculitis

Inflammatory disease of the arteries or veins or both leading to vessel wall injury, often with thrombosis or ischemic damage in the brain, spinal cord and meninges

Vasculitis = arteritis = angiitis

How to suspect CNS vasculitis?

Headache, encephalopathy, seizures,
persistent or intermittent neurological deficit
or stroke

and/or

Imaging findings varying from small ischemic
changes to infarction, hemorrhage, and high
intensity lesions in the white matter

Radiologic diagnostics in CNS vasculitis – a challenge

Diffusion weighted imaging (DWI)

CT-angiography

MR-angiography

Conventional angiography

Limited sensitivity and specificity

Small vessel vasculitis - difficult to detect!

High resolution MRI

Contrast with gadolinium

Defines vessel wall characteristics in CNS vasculitis and also in reversible cerebral vasoconstriction syndrome

Enhancement

Wall thickening

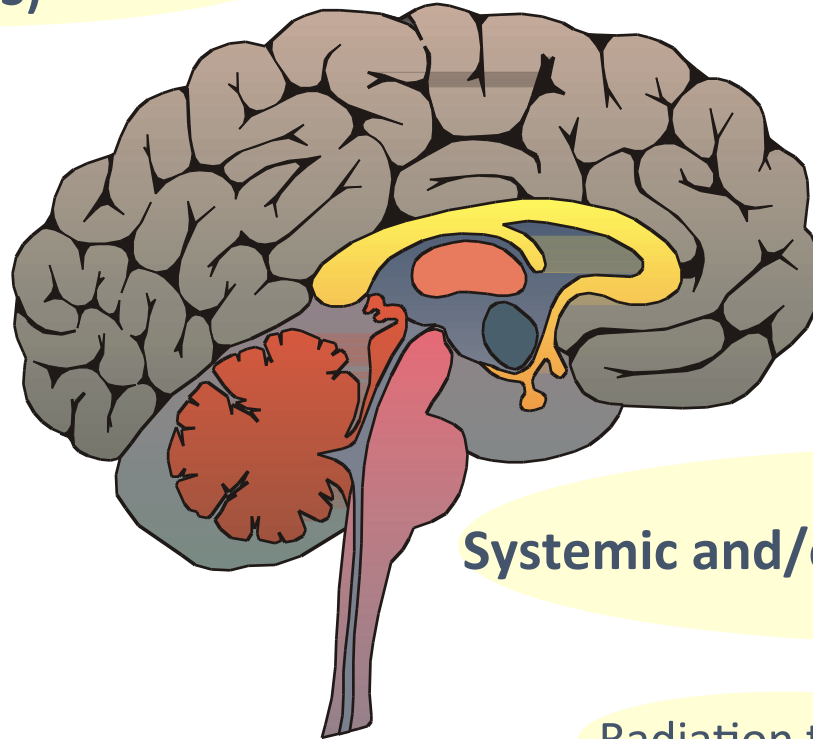
Lumen narrowing

Obusez et al, AJNR, 2014

Origin of CNS vasculitis

Primary CNS vasculitis
(PACNS)

Secondary vasculitis



Systemic and/or inflammatory disorders

Radiation therapy

Malignancy

Infectious CNS vasculitis

Drug use

Primary CNS vasculitis (PACNS)

Uncommon (2.4 cases/1 mill/year)

CRP, SR - usually not elevated

2/3 had pathological CSF: pleocytosis, elevated protein but normal glucose

MR- and CT-angiography show ischemic signs and/or hemorrhages

Exclude systemic, inflammatory and infectious causes

Conventional angiography pos 75%

Finally it is a biopsy diagnosis (brain and meningeal)

Different histological patterns

Boysson et al, 2014; Hajj-Ali et al, 2014; Salvarani et al, 2012; Berlit et al, 2014

CNS vasculitis secondary to systemic or inflammatory disorders

Most common diseases

SLE, Behçet's syndrome, PAN, sarcoidosis, eosinophilic granulomatosis with polyangiitis (EGPA, previously known as Churg Strauss), Sjögrens syndrome

Rare

Granulomatosis with polyangiitis (GPA previously known as Wegener granulomatosis), dermatomyositis, Mb Crohn

Very uncommon

Urticarial hypocomplementemic vasculitis, Cogan's syndrome, RA

CNS vasculitis secondary to systemic or inflammatory disorders

Usually the CNS vasculitis is a late manifestation of the systemic disease

Systemic signs and symptoms from various organs

Inflammatory markers positive

Biomarkers/antibodies specific for the underlying disease are often present

Infectious causes to CNS vasculitis

Viruses

Hepatitis C

TBE ?

Protozoan & nematodes

Malaria

Toxoplasma

Tenia soleum

Bacterial diseases

Treponema pallidum

Tuberculosis

Borrelia

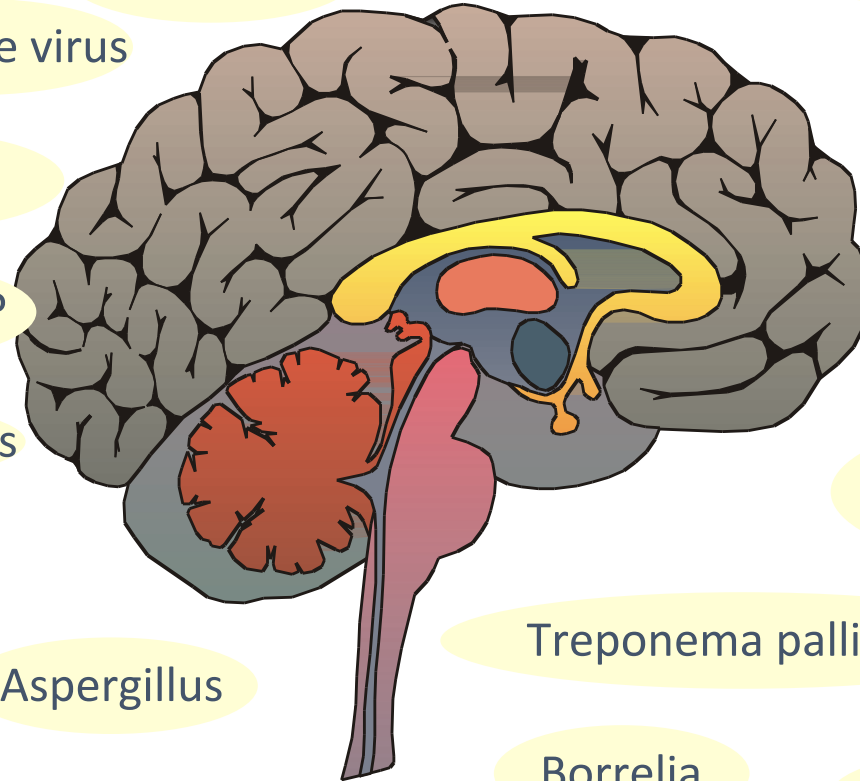
Meningitis

Nocardia

Rickettsia

Endocarditis

Bartonella



Fungi

Aspergillus

Histoplasma

Cryptococcus

Coccidioides

Mucormycosis

Nipah virus

VZV

CMV

HIV

Viral hemorrhagic viruses

West Nile virus

Dengue

Jap B encv?

Viruses

Hepatitis C

TBE ?

Protozoan & nematodes

Malaria

Toxoplasma

Tenia soleum

Bacterial diseases

Treponema pallidum

Tuberculosis

Borrelia

Meningitis

Nocardia

Rickettsia

Endocarditis

Bartonella

Fungi

Aspergillus

Histoplasma

Cryptococcus

Coccidioides

Mucormycosis

History in search of infection

Onset of CNS symptoms, insidious? acute?

Additional symptoms, weight loss? Fever?

Residency? Visit to other countries? (WNV, jap B-enc, malaria) Country of birth ? (tb)

Any special risk behaviour?

Tick- or mosquito bites or connection with animals?

Immunosuppression?

Drugs?

CNS vasculitis – experts involved

Pathologist

Infectious Diseases



Neurologist

Rheumatologist

Microbiologist

Neuroradiologist

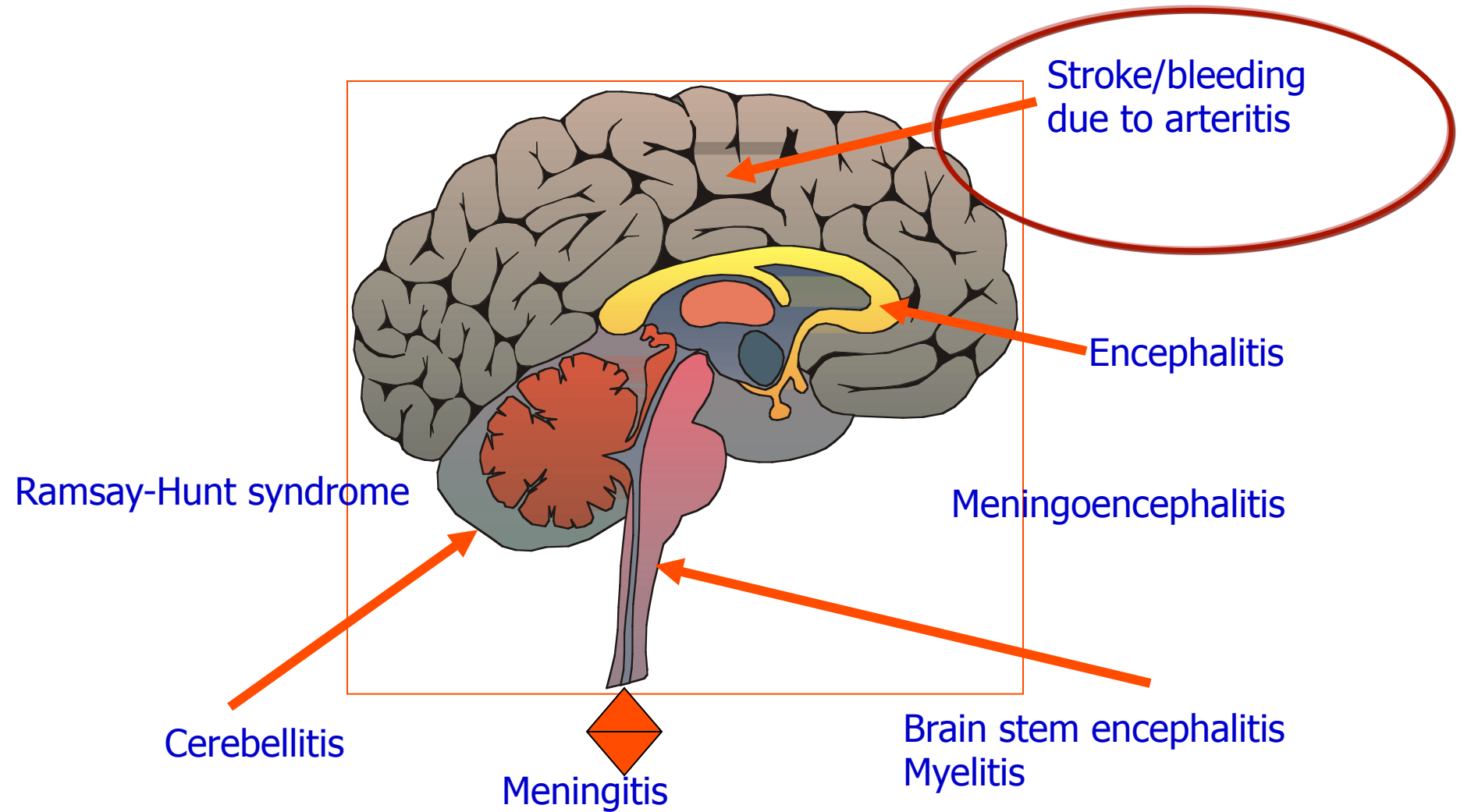
Microbiological tests

CSF culture, microscopy: bacterial, fungal
CSF 16SrRNA PCR
CSF multiplex bacterial PCR
Borrelia antibodies in CSF/serum
CSF VZV and HSV DNA PCR+ intrathecal antibodies
CSF CMV DNA PCR
HIV test
Syphilis diagnostics
Cryptococcus diagnostics
Toxoplasma serology, CSF PCR
Local flaviruses serology, PCR

If suspicion and epidemiology:

Flaviviruses (TBE, West Nile virus, Jap B enc virus, Dengue) serology, PCR
Malaria- thick and thin blood smear
TB diagnostics
Rickettsia serology

VZV and CNS clinical syndromes

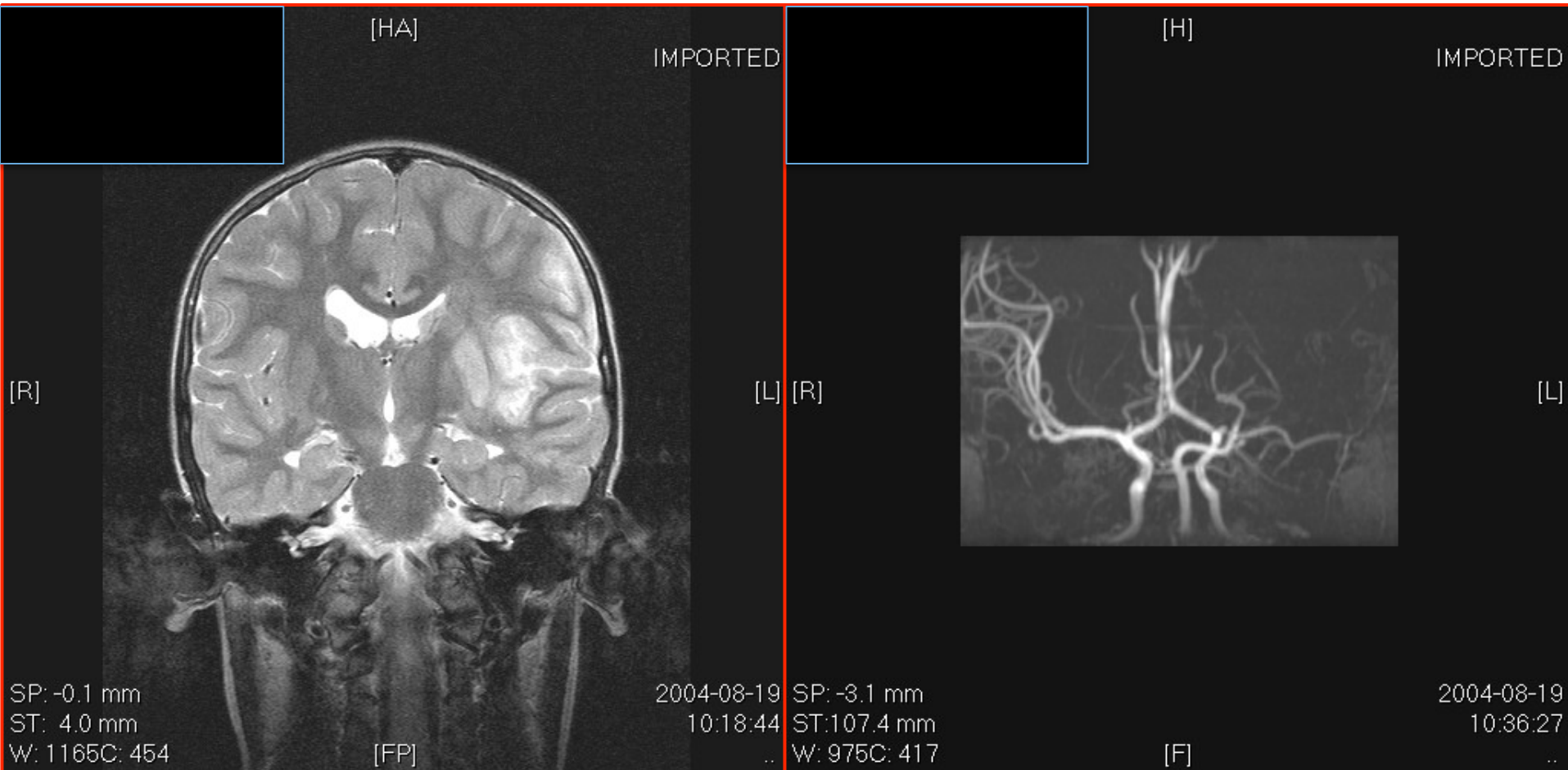


Case 1

- 4-year old boy with asthma, allergy against nuts
- 3 days before admission he had transient problems with his balance, dysarthria
- The actual morning headache, difficulties to speak, rightsided facial paralysis and rightsided hemiparesis

- Status:
- Somnolent, no fever, no neck stiffness
- Central facial paralysis, dysphasia
- Hemiparesis right side, pos Babinski right side

MRI and MR-angiography



- Lumbar puncture with thin needle:
- CSF-erythrocytes $335 \times 10^6 / L$
- CSF-leukocytes $34 \times 10^6 / L$, mainly mononuclear cells
- CSF-protein 117 mg/L - normal

Result from the Virology Department and treatment

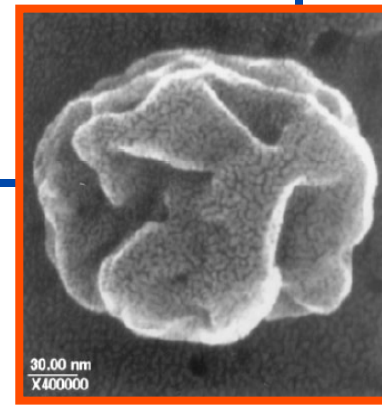
2 days later: VZV DNA was detected in the CSF by PCR

The boy had primary varicella infection 2 months ago, no actual blisters or skin lesions

Aciclovir i.v was started and continued for 5 days in addition to corticosteroids, ceftriaxone was stopped (after negative Borrelia serology in the CSF). Thereafter valaciclovir 500 mg X 3 orally

Serology VZV IgG 3200, no intrathecal antibodies

Diagnosis: varicella zoster virus vacsulitis in a. cerebri media sin, reactivated infection



Children and VZV-associated stroke

Stroke incidence : 1/15 000 cases of varicella

One third of pediatric ischemic stroke patients had varicella the year before

Transient ischemic attacks (TIA) and reinfarctions after varicella associated stroke

Over 70 case reports in the literature

Cases positive for VZV DNA in the CSF and/or VZV intrathecal antibodies and autopsy findings of VZV infection

Sebire et al, 1999; Braun et al, 2009; Ciccone et al, 2010; Askalan et al, 2001

Chickenpox and Risk of Stroke: A Self-controlled Case Series Analysis

Sara L. Thomas,¹ Caroline Minassian,¹ Vijeya Ganesan,² Sinéad M. Langan,¹ and Liam Smeeth¹

¹Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine; and ²Institute of Child Health, University College London, United Kingdom

560 individuals (including 60 children)

In children: 4-fold increased risk of developing stroke after chickenpox

In adults: less marked increased risk

Increased risk of stroke after herpes zoster

Retrospective epidemiological studies

30% higher risk of stroke than control group the first year after HZ (Taiwan)

4.3 fold higher risk of stroke after zoster ophthalmicus (Taiwan)

17% higher risk of stroke the first year after HZ (Denmark)

TIA and myocardial infarction increased after HZ (UK)

Significantly increased risk of stroke 1-26 weeks after HZ (UK). The risk decreased with antivirals

Kang et al, Stroke 2009; Lin et al, Neurology 2010; Sreenivasan et al, PLOS One 2013; Breuer et al, Neurology 2014; Langan et al CID, 2014

Evidence of arterial VZV wall infection and inflammation

Review



Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment

Don Gilden, Randall J Cohrs, Ravi Mahalingam, Maria A Nagel

Marie Studahl, Department of Infectious Diseases, Sahlgrenska University Hospital

Gilden et al, Lancet Neurol, 2009

Clinical spectrum of varicella-zoster vasculopathy

Large vessel granulomatous angiitis (acute hemiplegia after contralateral trigeminal zoster in adults) or postvaricella arteriopathy in children

Transient ischemic attacks

Ischemic and hemorrhagic infarctions

Multifocal VZV vasculopathy

Temporal arteritis mimicking giant-cell arteritis

Less common

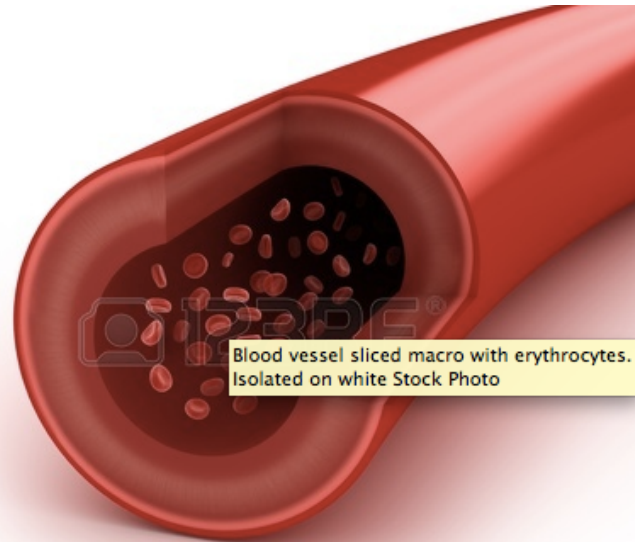
Subarachnoid and intracerebral hemorrhage

Arterial ectasia, aneurysm

Spinal cord infarction

CNS vasculitis

Large vessel



Small vessel

Medium sized vessel

Which CNS arteries are involved?

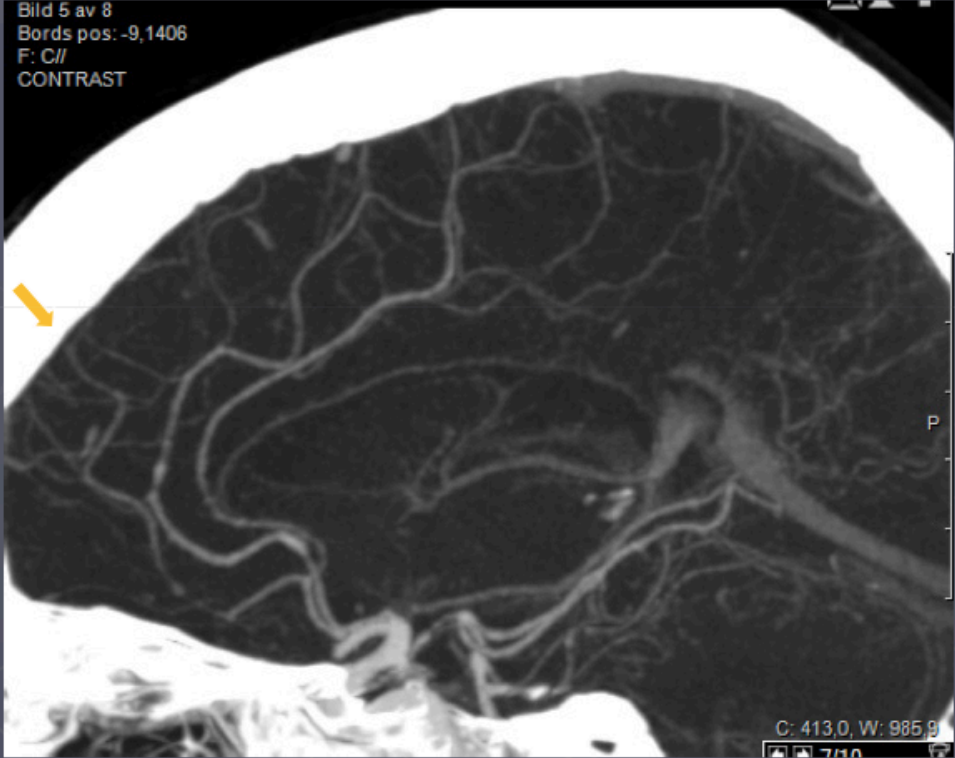
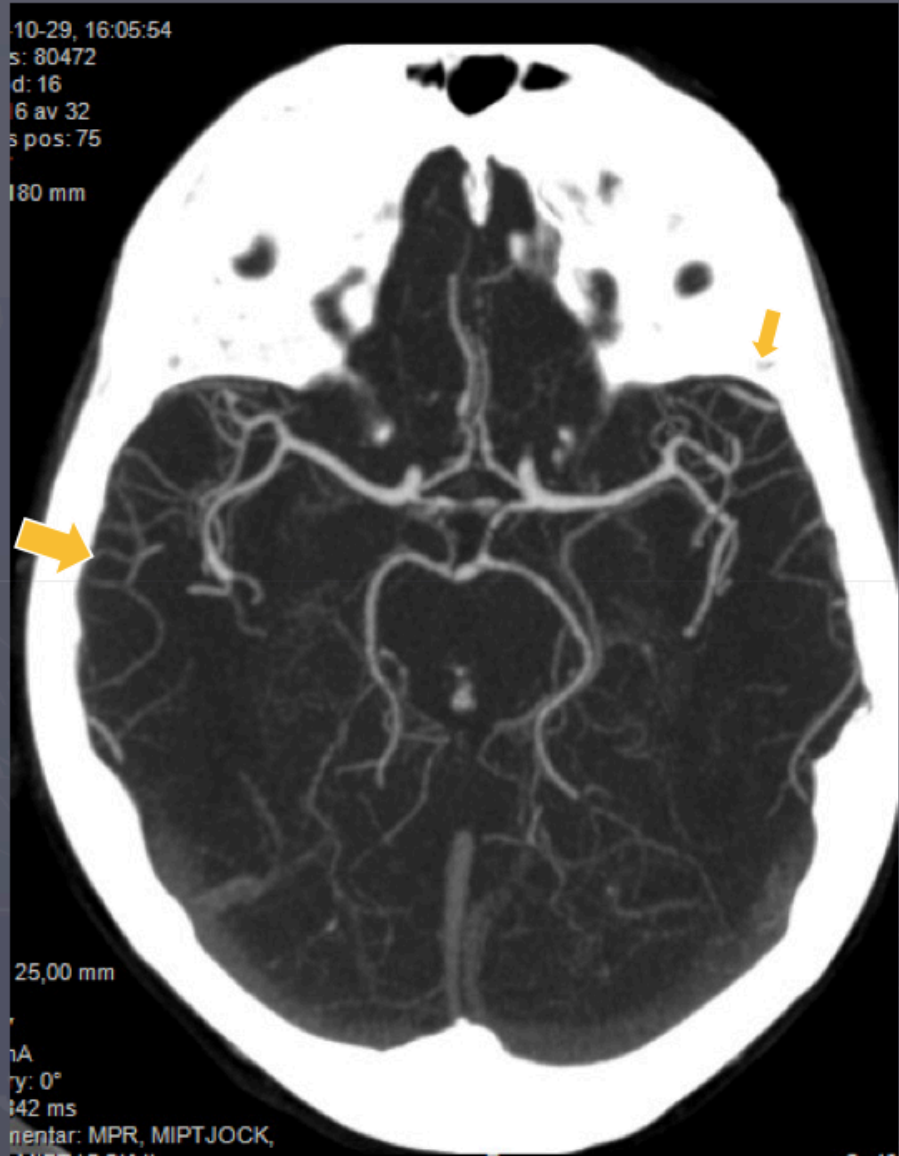
Previously multifocal small vessel vasculopathy was found in immunocompromised hosts

but

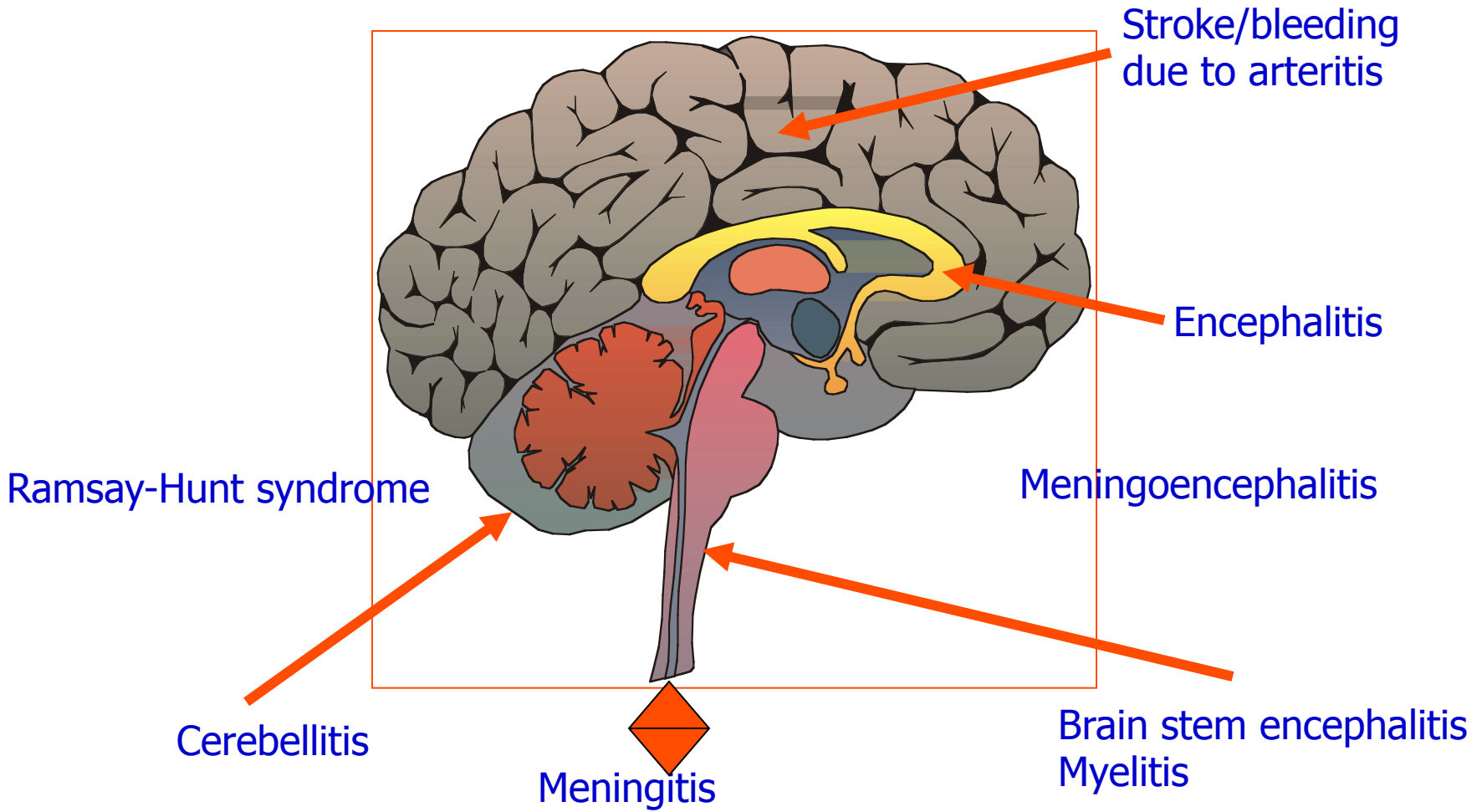
multifocal vasculopathy is seen in both immunocompetent and immunocompromised individuals

Nagel et al, 2008

69-year old woman with VZV CNS vasculitis



VZV and CNS clinical syndromes



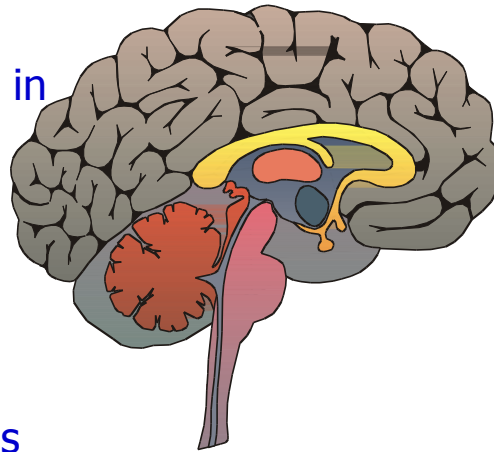
Zoster encephalitis - some or all cases caused by vasculitis?

Negative radiology, but also deep and cortical abnormalities, ischemic and hemorrhagic changes

No systematical studies performed on imaging in VZV CNS disease

Seldom virus or viral DNA found in brain parenchyma

Few autopsy studies performed



No suitable animal models

Mueller et al, Neurol Clin 2008; Gilden et al, Lancet Neurol 2009; de Broucker et al, Clin Microbiol Infect, 2012; Graneröd et al, Lancet Infect Dis, 2010; Grahn, thesis, 2013 <https://gupea.ub.gu.se/handle/2077/32398>

Ramsay-Hunt syndrome and facial paralysis only, 1995-2014, n= 41

23 F/18 M

Median 60 years of age (9 mo-89)

Symptoms:

Peripheral facial paralysis n=41

Dizziness, balance problems 23/39

Acute subjective hearing loss 16/39,
hyperacusis 1/39

Pain temporally, head or face 22/39

Blisters 21/41, no blisters 20/41

Onset of blisters: before 10, concomitant or after 7, 4 unknown

Blister location: auricular, mouth

Subfebrile or fever 13/39

Ramsay Hunt syndrome



Lindström J, Grahn A, Studahl M, unpublished data, 2014

VZV myelitis - some cases are caused by vasculitis

Rare in immunocompetent patients

Progressive and sometimes fatal in immunosuppressed patients

Unknown pathogenesis - in fatal cases invasion of VZV in parenchyma and nerve roots but **VZV may also cause spinal cord infarction**

Kleinschmidt DeMaster et al, Arch Pathol Lab Med, 2001; Devinsky et al, Brain 1991; Hung et al, J Neurol Sci, 2012

VZV CNS vasculitis underdiagnosed?

CSF is not examined (PCR and intrathecal VZV antibodies) routinely in adults (or children) with stroke symptoms

Preceding zoster rash is lacking (1/3)

Neurological symptoms may occur months after zoster or chickenpox

Problems with the diagnostics in VZV CNS vasculitis

Problem 1

If lumbar puncture is performed

No pleocytosis (1/3)

PCR VZV DNA in CSF is negative (2/3)

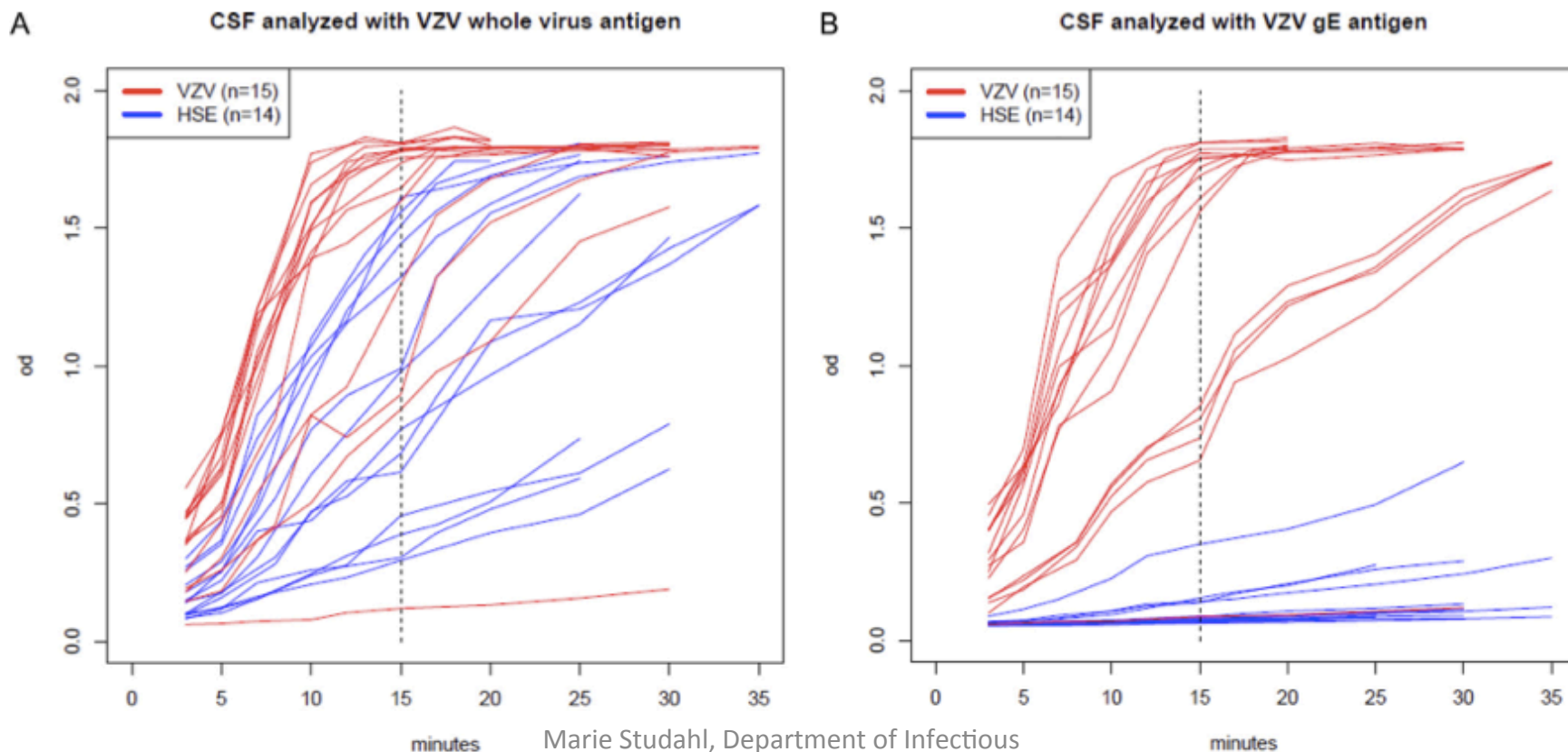
Therefore you need to analyse intrathecal antibodies which are found in high percentage

Problem 2

The antibodies crossreact with herpes simplex antibodies

Varicella-Zoster Virus (VZV) Glycoprotein E Is a Serological Antigen for Detection of Intrathecal Antibodies to VZV in Central Nervous System Infections, without Cross-Reaction to Herpes Simplex Virus 1

Anna Grahn, Marie Studahl, Staffan Nilsson, Elisabeth
Thomsson, Malin Bäckström and Tomas Bergström
Clin. Vaccine Immunol. 2011, 18(8):1336. DOI:
10.1128/CVI.05061-11.
Published Ahead of Print 22 June 2011.



Future directions in VZV CNS vasculitis

Biomarkers to detect vascular origin of CNS disease ?

Further pathogenetic studies in the different clinical syndromes caused by VZV

Development of more sensitive and specific imaging techniques ?

Randomised controlled trials with antivirals + immunosuppressive drugs for certain VZV CNS manifestations ?

Vaccination impact on CNS complications? (varicella and herpes zoster)

A photograph of a tree heavily laden with ripe, red apples. The leaves are green and dense, creating a lush background for the bright red fruit. The text "Thank you for listening!" is overlaid in the center in a large, white, sans-serif font.

Thank you for listening!

Marie Studahl, Department of Infectious
Diseases, Sahlgrenska University Hospital