CNS vasculitis of infectious origin

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Grenoble
ESCMID course
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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!

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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

Infectious CNS vasculitis

Radiation therapy

Malignancy

Drug use

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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

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 hypocomplementemtic 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.

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Infectious causes to CNS vasculitis

Viruses
- Nipah virus
- VZV
- CMV
- HIV
- Jap B encv?
- Dengue
- West Nile virus
- Hepatitis C
- TBE ?
- Viral hemorrhagic viruses

Protozoan & nematodes
- Malaria
- Toxoplasma
- Tenia soleum

Bacterial diseases
- Tuberculosis
- Meningitis
- Tenia soleum
- Bartonella
- Endocarditis
- Rickettsia
- Nocardia
- Treponema pallidum
- Borrelia

Fungi
- Histoplasma
- Aspergillus
- Cryptococcus
- Coccidioides
- Mucormycosis

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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

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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

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VZV and CNS clinical syndromes

- Cerebellitis
- Brainstem encephalitis
- Myelitis
- Encephalitis
- Stroke/bleeding due to arteritis
- Meningitis
- Ramsay-Hunt syndrome
- Meningoencephalitis

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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
• 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
560 individuals (including 60 children)

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

In adults: less marked increased risk

Thomas et al, CID, 2014
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 opthalmicus (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


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Evidence of arterial VZV wall infection and inflammation

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

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

Medium sized vessel

Small 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

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- Brain stem encephalitis
- Myelitis
- Encephalitis
- Meningoencephalitis
- Meningitis
- Stroke/bleeding due to arteritis
- Ramsay-Hunt syndrome

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Zoster encephalitis - some or all cases caused by vasculitis?

- Negative radiology, but also deep and cortical abnormalities, ischemic and hemorrhagic changes
- Seldom virus or viral DNA found in brain parenchyma
- No systematical studies performed on imaging in VZV CNS disease
- Few autopsy studies performed
- No suitable animal models

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

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

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

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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

Published Ahead of Print 22 June 2011.

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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)
Thank you for listening!

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