Pediatric Acquired Demyelinating Disorders

ADEM and MS

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ADEM - Acute Disseminated Encephalomyelitis Syndrome

- Immune mediated disease of the CNS - involvement of white matter
- Form of neuroallergy
- It occurs following infection or vaccination
- Autoimmune demyelination - multiple inflammatory lesions in the brain and spinal cord
ADEM - Epidemiology

- Incidence 1,5 - 3:100 000
- More frequent in children and adolescents
- Gender: predominance in boys
- Worldwide in all races
- Seasonal incidence in winter from October to March
ADEM – Causes and Antecedent History

- Infections thought to induce ADEM:
  - **Viral:**
    - HSV, EBV, CMV, HHV6, Hepatitis A, B
    - Varicella, Influenza, Coxsackie, Measles,
  - Smallpox
  - **Bacterial:**
    - Streptococci, Salmonella, Chlamydia, Borrelia, Legionella, Mycoplasma Leptospira
  - **Vaccination** with risk of ADEM onset:
    - Rabies, Influenza, Rubella, Measles, BCG, Meningitis A+C
    - Hepatitis A+B, Diphtheria, Tetanus, Pertussis
ADEM - Pathogenesis

- No evidence of infectious agent in the CNS tissue
- Immune reaction mediated by autoreactive T lymphocytes against MBP, PLP
- Molecular mimicry
- Polyclonal activation of T cells by superantigens
- Inhibition of suppressor T cells
- Direct destruction of oligodendrocytes
- Genetic susceptibility
ADEM- Histopathological Changes

- Similar to experimental allergic encephalomyelitis (an animal model)

- Perivenous demyelination foci, infiltration of lymphocytes and macrophages, hyperemia, perivascular edema, hemorrhage

- Changes along the small blood vessels in the white and gray matter (BG, thalamus, cortex)

- Recovery — glial and fibrotic scars
ADEM - Clinical Manifestations

- **Prodromal symptoms** 1-2 weeks after infection:
  Fever, headache, vomiting, meningismus, somnolence

- **Neurological symptoms:**
  Encephalopathy: irritation, lethargy, altered consciousness, epileptic seizures
  Dysphasia, hemiparesis
  Ataxia, tremor, nystagmus
  Optic neuritis
  Facial palsy
  Transverse myelitis

- **Atypical variations**: subclinical × fulminant
ADEM - Paraclinical Examinations I

- Elevation of **inflammatory markers** FW, CRP, leucocytes
- EEG diffuse slow activity, focal epileptiform activity
- CSF normal or protein - cytological association
elevated IgG index, rarely oligoclonal bands
ADEM - Paraclinical Examinations II

- Abnormal brain MR demonstrating:
  - multiple lesions in the cerebral white matter
  - larger than 1-2 cm, diffuse poorly demarcated
  - number, location and size are variable, but same age (x MS)
  - Brainstem, cerebellum, subcortical
  - In grey matter: thalamus, BG (x MS)
  - T2W hyperintense, few or no T1 hypointense (x MS)
  - No new clinical and MRI findings emerge 3 months or more after onset
  
  (x MS: DIT + DIS)
ADEM – MRI

Diffuse poorly demarcated large lesions involving cerebral white matter with hemorrhagic component
ADEM - Clinical Forms

- **Monophasic event**
  
  Acute demyelinating (ADEM)
  Acute hemorrhagic leukoencephalitis (AHLE)  2%

- **Multiphasic event**  1- 4% (MDEM)
  Often relapses after quick withdrawal of corticosteroids
ADEM - Differential Diagnosis

- Multiple Sclerosis
- Acute viral encephalitis (HSE)
- CNS vasculitis
- Tumor, CNS lymphomas
- Leukodystrophy, mitochondrial encephalopathy
- Progressive multifocal leukoencephalopathy (HIV)
- Systemic lupus erythematosus
- Neurosarcoidosis
## Differentiation ADEM x MS

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ADEM%</th>
<th>MS%</th>
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<tbody>
<tr>
<td><strong>Trigger factors</strong></td>
<td>74</td>
<td>38</td>
</tr>
<tr>
<td><strong>Polyfocal signs</strong></td>
<td>91</td>
<td>38</td>
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<tr>
<td><strong>Encephalopathy</strong></td>
<td>69</td>
<td>15</td>
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<tr>
<td><strong>Epileptic seizure</strong></td>
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<tr>
<td><strong>Leucocytosis</strong></td>
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<td>22</td>
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<tr>
<td><strong>Pleocytosis</strong></td>
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<td>42</td>
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<tr>
<td><strong>Elevated CSF protein</strong></td>
<td>60</td>
<td>33</td>
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<tr>
<td><strong>Oligoclonal bands</strong></td>
<td>29</td>
<td>64</td>
</tr>
<tr>
<td><strong>PV lesions on MRI</strong></td>
<td>44</td>
<td>92</td>
</tr>
</tbody>
</table>
ADEM - Therapies

- Aggressive treatment !! Evidence to favorable outcomes !
- **Corticosteroids** pulse therapy 10 - 20mg/kg/dose 3 - 5 days followed by short taper

- **Immunoglobulins** 0.4g/kg daily - 5 days
- Symptomatic therapy (AED, antiedematous, anti-infective)

- **Plasma exchange** - fulminant cases

- ICU monitoring, nursing
- Psychotherapy, physiotherapy
ADEM Case Report  Joseph  *2003

**Vaccination**  TetraHib  15.12.2008  (DiTePe + H.influenzae)

19.12.2008 **Gastroenteritis**

29.12.2008 Generalised epileptic seizure

   Paraparesis, urinary retention

Transport to the Dpt. of Child Neurology Motol
ADEM Case Report  Joseph  *2003

- **MRI**  brain - multiple inflammatory lesions
  
  spinal cord – myelitis C3-C5

- **CSF**  leuco 88/3   protein 322 mg/l   normal i.t.IgG

- **Serology**  negative

- **EEG**  bilateral slowing PO

- **Therapy**  i.v acyclovir, methylprednisolone,diazepam

- **Outcome**  : full recovery after 6 months
ADEM Joseph *2003

After 2 months = 3/2009
MRI brain and SC: lesions regression
Mild paraparesis
ADEM - Prognosis

- Better in children than in adults
- Gradual adjustment
- Full recovery is seen in 50-75% of cases after 1-6 months
- In 30% of cases lasting residual changes
  (mental retardation, focal deficit, epilepsy ..)
- Mortality 5 – 10%
- 20% later diagnosed with MS
Pediatric Multiple Sclerosis (MS)

Chronic inflammatory autoimmune disease

The myelin sheaths around the axons are damaged, leading to:

- demyelination
- axonal loss
- neurodegeneration
- CNS atrophy

Occurrence in young adults - average age approx. 30 years
Onset during childhood or adolescence is increasingly recognized
MS – Multifactorial Disease

- **Genetics** – polygenic inheritance
  The role of multiple genes in the pathogenesis
  The gene for APO E, osteopontin, olig1
  Predisposition HLA-DR2, DQ

- **Infections** – herpes viruses (EBV, HSV, HHV6)

- **Vaccination** is massive antigenic stimulation

- **Environmental factors - higher risk**
  geographical – in areas farther from the equator
  decreased vitamin D - less exposure to the sun
  severe stress
  smoking
MS Incidence

1.1 million patients in the world

In the Czech Republic

170 – 200 / 100 000 inhabitants
MS - Autoimmunology

Immune – mediated disorder
Targets of immune response - myelin sheaths (MBP + PLP)
Destruction of oligodendrocytes
T cells recognize myelin as foreign attack
   proliferation CD3+, CD8+ Tcells
Cytokine release IL1,2,12, IFNgama, TNF a,b
BBB becomes permeable
Formation of inflammatory lesions
Thinning or complete loss of myelin
Transsection of the neuron axons
Axonal loss - Schema

- Activated T cell
- Cytokines
- Chemokines
- MMPs
- Abs + complement
- T cell
- NO
- MMPs
- TNF-α
- CD8+ T cell and perforin
- Na⁺ channel up-regulation
- Disturbed axon-ganglia interaction
- Ca²⁺ influx
- Ca²⁺ channels
- Loss of trophic support
MS - Pathophysiology

- Demyelination lesion in MS
- The immune cells in plaque - scar – sclerae (sclerosis)
Neuroimmune Balance

- **Proinflammatory and neurotoxic factors**
  - Th1 cytokines
  - TNF
  - IL-1
  - Osteopontin
  - Leukotriens
  - MMP
  - NO, glutamate
  - Neurodestruction

- **Anti-inflammatory and neuroprotective factors**
  - Th2 cytokines
  - TGF
  - Neurotrophic factors:
    - BDNF, NT
    - some prostaglandins
  - Neuroprotection
MS - Clinical Manifestations

- In 1868 Jean-Martin Charcot described the Charcot’s triad
  nystagmus, intention tremor, scanning speech

- **Main symptoms:**
  - Sensory symptoms 46%
  - Motor - “ - 20%
  - Optic neuritis 17%
  - Brainstem 13%
  - Ataxia 14%
  - Bladder and bowel difficulties
  - Cognitive impairment, emotional lability, fatigue
  - Seizures (corticosubcortical lesions) 2-5%

- **EDSS** Expanded Disability Status Scale
**MS - Clinical Courses**

**CIS** an attack suggestive of demyelination does not fulfill the criteria for definite MS

**Benign** 20%
- low number of attacks, minimum disability
- EDSS under 3.0 at 15 years duration of illness

**Relapsing remitting** episodic periods of worsening 70%

**Secondary progressive** gradual progressive neurologic decline between acute attacks

**Primary progressive** 10% without remission after initial MS symptoms
2010 McDonald MRI Criteria

**DIS** can be demonstrated by one or more T2 lesion in at least 2 areas:

- Periventricular (PV)
- Juxtacortical (JC)
- Infratentorial (IT)
- Spinal cord (SC)

**DIT** can be demonstrated by:

1. A new T2 and/or Gd enhancing lesion(s) on follow-up MRI
2. Simultaneous presence of asymptomatic Gd enhancing and nonenhancing lesions at any time
MRI

OVOID lesions larger 6 mm
Typical localization: PV, JC, IT, SC
Hyperintense in T2W - inflammation, demyelination
Black holes in T1W - axonal loss

Mandatory application of gadolinium!

Reason to indicate: activity assessment process
What other tests?
Paraclinical Examinations: CSF, EP

- **CSF**: Lymphocytes - mononuclear cells, plasma cells
  - The count under 100/mm³
  - 2 OCB that are not in the serum (in 85% - 95% pts.)
  - Increased IgG index

- **Evoked potentials**: Slow conduction
  - Abnormal latency, amplitude, shape

  \[ \text{VEP} > \text{MEP} > \text{SEP} \]

  (According to the clinical significance)
Pattern VEP

VEP: Pattern VEP 4ch

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<tr>
<th>Channel</th>
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<th>V/D</th>
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<tr>
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<td>Right (O3-Czdax)</td>
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EOAMS

Onset before 16 year

Approximately 5% from MS population 0,4 - 5,6%

**Infantile** – under 10 years of age: very rare 0,5%

**Juvenile** – over 10 years of age
MS Therapies

- You have to treat **early** and aggressive
  Early initiated long term therapy is safe and is related to better outcomes!

- **Steroids** – for symptomatic attacks – iv methylprednisolone 3-5 g

- **Disease-modifying treatments:**
  - Interferon beta-1a, interferon beta -1b
  - Glatiramer acetate
  - Natalizumab - a humanized monoclonal antibody
  - Fingolimod - since 2010 the first oral drug
  - Teriflunomide - since 2012 oral drug

DMD reduce the progression rate of the disease, but do not stop it.

- **Multidisciplinary approach** – symptomatic therapy
- **Neurorehabilitation**
Differences

**POMS - Pediatric Onset MS**
- Ratio female/male: 0.8
- Polysymptomatic onset
- Initial symptoms:
  - Brainstem, cerebellar
  - Seizures: 22%

**AOMS - Adult Onset MS**
- Ratio female/male: 2-3
  (Sex hormones have regulatory role)
- Monosymptomatic onset
- Sensory, motor
- Seizures: 5%
Course of EOEMS

- Frequent relapses, 40-60% have a relapse after 1st attack up to 1 year

- Mild benign form in 90% cases, only 3% PP
  - Less cumulative disability after 10 years of illness

- EDSS lower (4 - 4.5)

- The progression of disability is slower than in adults
  - The developing CNS has more plasticity to recover

- MRI - giant lesions, T1W black holes

- Atrophy of the brain develops slowly

- Cognitive difficulties present
MRI Brain Atrophy 1998-2004
Prognosis of EOMS

- **Unpredictable, the risk always!**
- **Worse prediction:**
  - High relapse rate in the first 2 years
  - Short interval between attacks
  - Residual disability in initial symptoms
  - Early entry into the secondary progression
  - Sphincter difficulties
  - Paraclinical activity: MRI with Gd enhancement
Case Report - Mike - disease onset at age 4

**Family History**: mother - thyreopathy

**Personal History**: obesity 50 kg

**First symptoms**: brainstem, nystagmus, vertigo, ataxia

**MRI**: multifocal lesions in the white matter, Gd enhancement in 1/04 progression – dissemination in time and in space

**CSF**: 29/3 pleocytosis, OCB 4

**VEP**: abnormal

**MEP**: patol.
Case Report - Mike - disease onset at age 4

Course: RR form
Aggressive start - 3 episodes during first 3 months

Dg: infantile MS

Therapy: corticosteroids, azathioprine, IVIG
    current treatment: Copaxone

EDSS: 2,0
Case Report – Michaela with IDDM and MS

Family History: negative

Personal History: IDDM from 8 years

First symptom: paresthesia and cramps PHK at 11 y.

MRI: multiple demyelination periventricular lesions
CSF: OCB 5
VEP: abnormal, prolonged latency P 100
CR - Michaela with IDDM and MS

**Therapy**: methotrexate, IVIG
Methylprednisolone pulses, insulin pump

**Course**: RR form

**Dg**: IDDM, juvenile MS

**EDSS**: 3.0 cerebellar syndrome
- sphincter difficulties
- left sided hemiparesa
Thank you for your attention

Pelican is a symbol of our faculty.......