Important aspects and implications of selected CNS infections in children

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Overview

- Introduction
- TBE
- HSVE
- Relapsing- HSVE versus Post-HSVE associated with NMDAR antibodies
- Neuroborreliosis

Spectrum of inflammatory diseases of the CNS in children

1. Infectious diseases
   a.) viral
   b.) bacterial
   c.) fungi
   d.) parasites
2. Demyelinating-inflammatory diseases
3. Antibody- mediated autoimmune-encephalitis

TBE- case 1

- A 13 year old girl presented to the outpatient department with a 2-day history of fever up to 40°C, severe headache, nausea.
- The week before she had a five day episode of fever and general malaise.
- Previously healthy girl, fully immunized including TBE.
- One day after admission she became unconcious, was transferred to the ICU, ventilated.

TBE- investigations

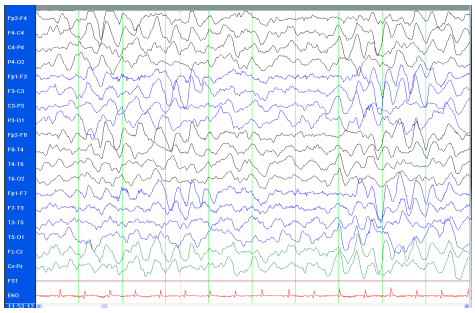
Cerebral-spinal fluid (CSF) studies:

- Glucose 72 mg/dl (60 - 80)
- Protein 750 mg/l (150 - 450)
- Leukocytes 227 Zahl/ul (0 - 4)

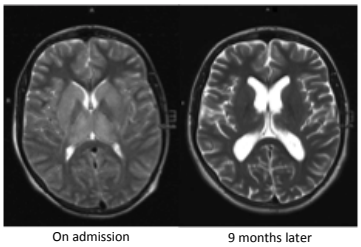
EEG: diffuse and intermittent frontal rhythmic delta slowing.

MRI: leptomeningeal contrast medium enhancement and grey matter involvement of the basal ganglia.

TBE- EEG



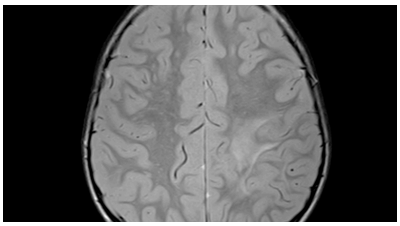
TBE- MRI studies show a spectrum of lesion patterns such as bilateral involvement of the thalamii



On admission 9 months later

TBE-case 2

- 6 yo boy with fever, nausea, vomiting, tonic-clonic seizures,severe headache, CSF 225 cells/ul,



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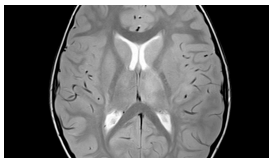
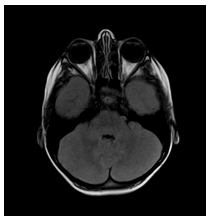
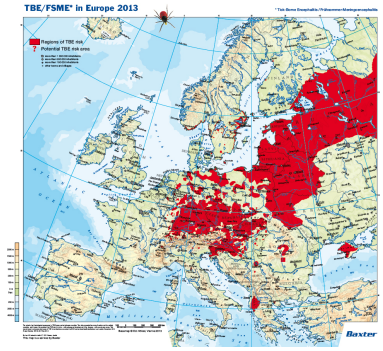




TBE- diagnostic criteria

- ✓ Biphasic course with fever and symtom free interval, then clinical symptoms of a meningitis or meningoencephalitis (e.g. altered mental status, focal neurological signs) and EEG changes with slowing of background activity.
- ✓ CSF pleocytosis (>5 cells/µl)
- ✓ Serological presence of virus-specific IgM in the acute phase and conversion to virus-specific IgG in a follow-up sample at least two weeks later.



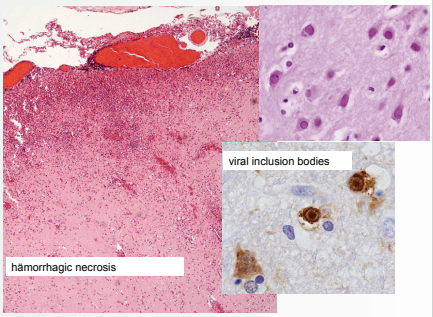
TBE

- In the majority of cases the disease follows a benign course.
- Few children suffer from severeneurological morbidity and even mortality.
- Even in non-severe cases MRI changes in particular in the thalamii can be found.
- In endemic areas it is strongly recommend to immunize also children against TBE.

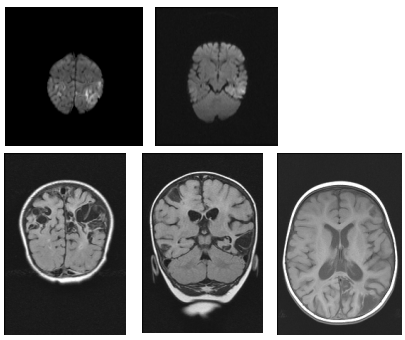
HSVE- case 1

- 8 months old girl with fever (39°C) and upper respiratory tract infection was admitted to the emergency room with a first convulsion lasting 20 minutes.
- Family history of febrile seizures positive; child was well and discharged.
- 2 days later readmission with fever and complex focal seizures lasting 5 minutes.
- CSF: HSV-PCR positive, cell count 234/ul.

Neuropathology of HSVE



HSVE- MR-imaging



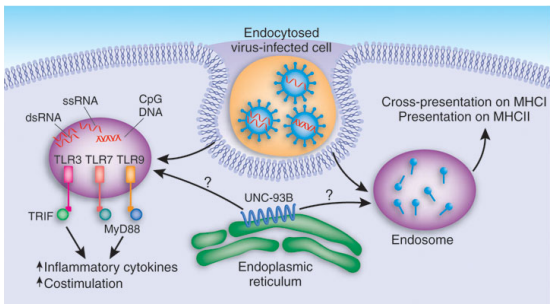
Relapsing HSVE in a young child

- video

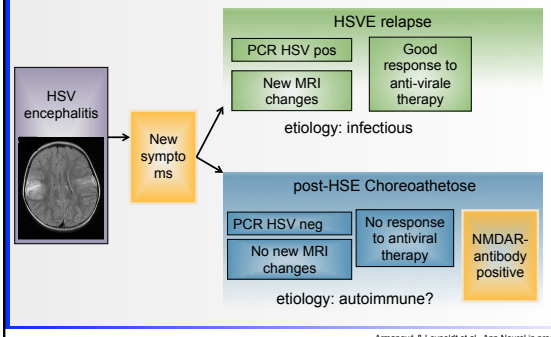
Genetics and HSVE

- In children with a family history of HSV infections such as encephalitis mutations in genes of the innate immune system have been found (e.g. TLR3, Science 2007; Unc93B, Science 2006).
- Leading to an inability of lymphocytes to produce high amounts of αIFN.
- Interestingly risk of relapses not significantely increased.

Toll like receptors

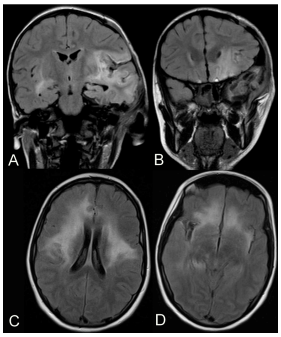


Post-HSV Encephalitis and NMDAR antibodies



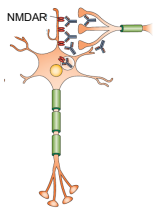
Armangué & Leypoldt et al., Ann Neurol in press

MRI findings in children HSVE relapse and a positive CSF-PCR



(Schleede et al., 2013)

NMDAR-Encephalitis



Antibodies cause a functional impairement of neuronal cells thorough internalisation of receptors!!

Good reponse to therapy!

Clinical worsening

Prodromi

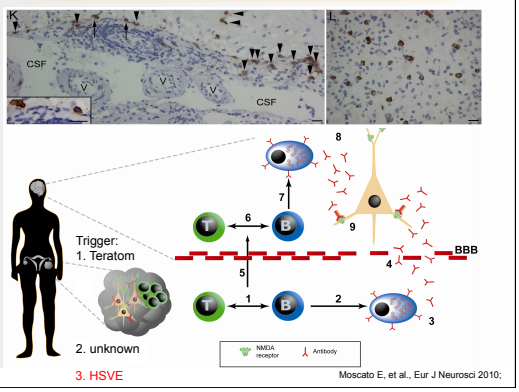
Agitation, psychosis, catatonia, memory problems, abnormal movements, seizures

coma, hypoventilation, +/- dysautonomia

Clinical improvement

Lancaster et al, Nat. Rev. Neurol 2012

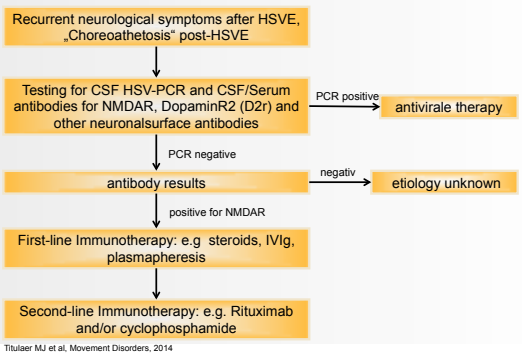
Pathogenesis of anti-NMDAR- encephalitis



Moscato E, et al., Eur J Neurosci 2010;

Post-HSV Encephalitis and NMDAR antibodies (patient videos)

Algorythm: Therapy and Diagnosis of post-HSVE



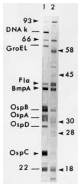
Titulaer MJ et al, Movement Disorders, 2014

Neuroborreliosis

Diagnostic criteria (German Society of Neurology):

- Typical clinical symptoms such as with meningitis, peripheral 7th nerve palsy or Bannwarth-Syndrome
- positive serology of IgM, IgG antibodies, positive Immunoblot (IB)
- CSF-pleocytosis (>20 cells/µl) +/- intrathecale abs synthesis of IgG and IgM abs against B. *burgdorferii*

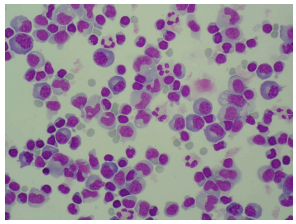
Therapy: 14 days i.v Rocephin/Cefotaxim



Pos.IB)

Neuroborreliosis

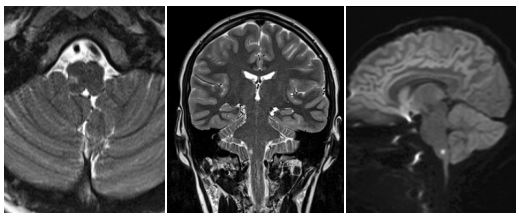
- CSF pleocytosis is characterized by the presence of a variety of different inflammatory cells (plasma cells, macrophages, lymphocytes)



Neuroborreliosis- case 1

- 14 year old boy who presented with gait unsteadiness after getting up in the morning
- Neurological examination: Small pupil and a mild ptosis on the right (Horner´s syndrome), right sided ataxia and a tendency to fall to the right, deviation of the soft palate to the left, hoarse voice and a hypoaesthesia of the left side of the body and face.

Acute brain stem infarction in neuroborreliosis



- The MRI showed a right sided dorsal lateral medullary infarction
- Diagnosis: Wallenberg syndrome or posterior inferior cerebellar artery syndrome.

Neuroborreliosis- case 2

- 16 yo boy developed a bilateral weakness in arms and legs, he had no pain, no bladder dysfunction.

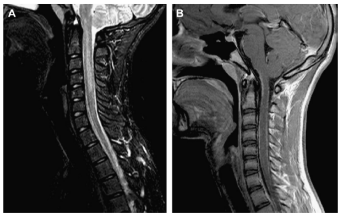


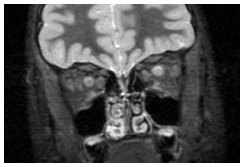
Fig. 2 – Spinal MRI of Case 2 shows (A) a lesion ranging from the pons down to C5 in the sagittal T2-weighted image and (B) leptomeningeal contrast enhancement in the sagittal T1-weighted image.

Neuroborreliosis- case 2

- Spinal MRI: longitudinally extentive transverse myeliti (LETM), meningeale enhancement!
- CSF: Protein 109mg/dl, 442 cells/µl.
- IgM und IgG antibodies against Borrelien present
- B. burgdorferii-IgG- Antibody index (AI) elevated!

Neuroborreliosis- case 3

- 9 year old girl with bilateral visual loss, pain on eye movement, colour vision impaired,
- CSF-pleocytosis; serum positive for IgM antibodies against B. *burgdorferii*.



- Diagnosis: bilateral optic neuritis

Neuroborreliosis and Neurocognition

- In adults with neuroborreliosis several studies indicate that longterm sequelae such as attentional difficulties, depression are increased. (Fallon et al., 1999)
- In children intellectual skills, memory and executive functions after NB are within the normal range. Behavioral or psychiatric problems are not more frequent compared to normal controls. (Zotter et al., 2013).