CNS complications of Viral Infections and Vaccines

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Mediated by **autoimmune mechanisms** (vs. direct CNS invasion by organism).

- PNS counterpart - Guillain-Barré syndrome.

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM)

- **monophasic** inflammatory demyelinating disorder that begins ***within 6 weeks*** of antigenic challenge (infection or immunization).

- *considerable overlap* in epidemiological, pathological, pathophysiological, clinical, CSF, imaging features *between ADEM and MS* - difficult to distinguish between two when encountering patients with single demyelinating event.

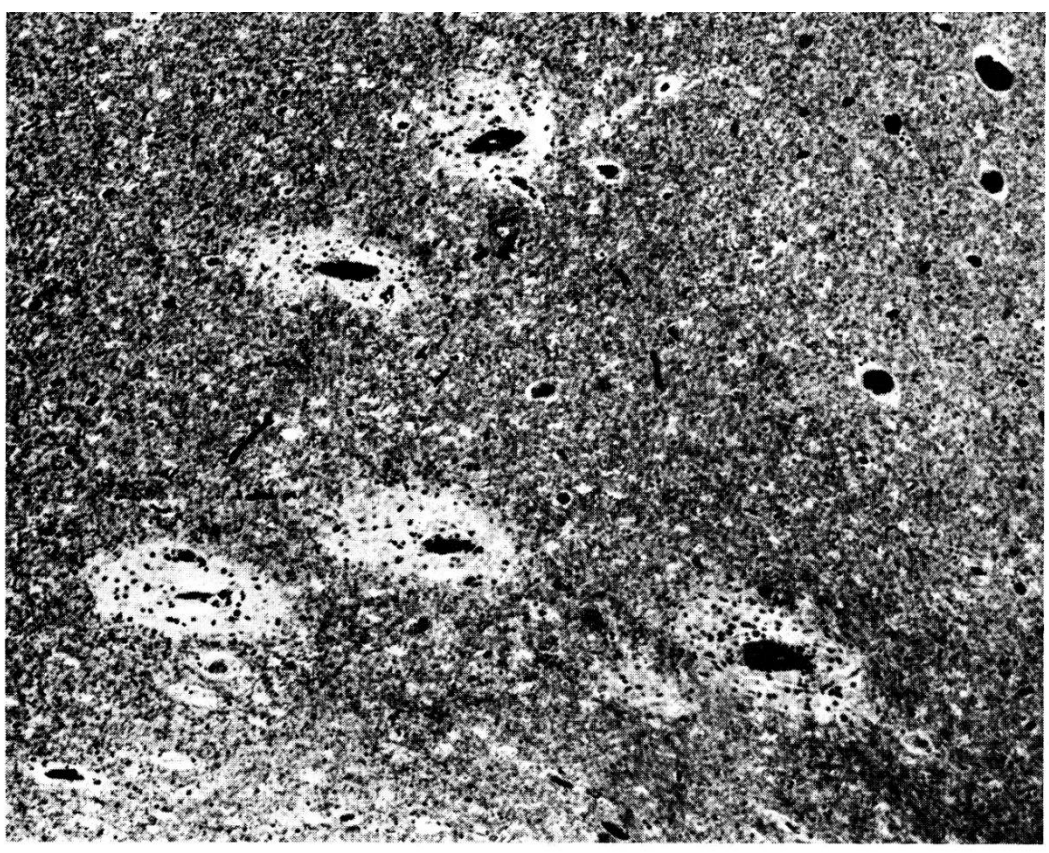
PATHOPHYSIOLOGY

- transient cell-mediated autoimmune response toward myelin (e.g. myelin basic protein).

- infections and vaccinations induce ADEM by ***molecular mimicry*** or by nonspecific ***activation of autoreactive T-cell clones***.

Histology - perivenous inflammation-edema-demyelination with relative preservation of axons.
PERIVENOUS DEMYELINATION !!!

- lesions commonly enlarge and coalesce, forming lesions pathologically indistinguishable from MS.
- repair occurs through remyelination.



Postvaccinal encephalomyelitis. Note demyelination (lack of stain) around venules (stained black) (Woelcke stain).

ETIOLOGY

a) **VACCINES** - **POSTVACCINAL ENCEPHALOMYELITIS** (3-6% of all ADEM cases).
- only epidemiologically and pathologically proven association is with *rabies vaccination*.
  - original Pasteur rabies vaccine (prepared in *rabbit spinal cord* - was contaminated with CNS tissue) had ADEM incidence 1 per 3,000-35,000 vaccinations.
  - use of *human diploid cell lines* (contain no nervous system tissue) for production of rabies vaccine has virtually eliminated risk of ADEM.

b) **INFECTIONS** - **POSTINFECTIOUS (S. PARAINFECTIOUS) ENCEPHALOMYELITIS**
- most commonly *nonspecific upper respiratory tract infection*.
- *measles* carries highest risk (1 per 1,000 cases) for ADEM among specific infections; now measles-related ADEM is rare (ADEM is now most frequently associated with varicella-chickenpox infections).

EPIDEMIOLOGY

- any age but most common during **childhood** – 80% cases during 1st decade, < 20% - during 2nd decade (i.e. earlier than MS), < 3% - adulthood.
- INCIDENCE during first-decade ≈ 3 cases per 100,000.
- cases occur in all regions of world.
- males = females.

CLINICAL FEATURES

- parainfectious ADEM usually *follows onset* of infectious illness (often during recovery), but because of latency of some pathogens ADEM *may precede* clinical symptoms of infection or two may *occur simultaneously*.

Viral PRODROME (few days) - headache, low-grade fever, myalgias, malaise.
Prodrome absent in MS! Also absent in 7-15% ADEM cases!

- hiatus between onset of viral prodrome and onset of ADEM may range 2-30 days.
- prodrome and ADEM are typically separated by phase of recovery from fever and other constitutional manifestations.

Neurological symptoms develop very rapidly (hours ÷ several days*) - irritability and lethargy, delirium (encephalopathy of varied degree), changes in mental status up to coma (88%), headache (55%), focal or generalized seizures (25%), meningismus (25%). *rarely up to 6 weeks

Prominence of cortical signs! (vs. MS)

- fever returns in ≈ 50% cases.
- variety of **multifocal neurological manifestations** (brain, brain stem, cerebellum, optic nerves, spinal cord).

ADEM - classically **multifocal** involvement at onset;
vs. MS often presents with **monosymptomatic** deficits.

  - ADEM-associated optic neuritis is usually bilateral (vs. MS).
- peak severity occurs within several days → recovery begins soon afterward.

ADEM is typically *monophasic* disease of **prepubertal children**;
vs. MS is chronic *relapsing-remitting* disease of **young adults**.

DIAGNOSIS

CSF – although ***oligoclonal IgG bands*** occur transiently in 1/3 cases, their persistence implies diagnosis of MS!

- subsequent disappearance of bands is evidence against MS.
- ***myelin basic protein*** concentration↑ (reflects demyelination).
- ***mononuclear pleocytosis*** of 20-200 cells/mm^3.

MRI – identical to MS (basal ganglia or cortical lesions, large globular white matter lesions are more frequent in ADEM; 90% ADEM lesions disappear with time).

- characteristic centrifugal **"cotton-ball"** lesions at *junction of deep cortical gray and subcortical white matter* are found in 90% cases.
- classically *all ADEM lesions develop simultaneously*! (90% lesions enhance with gadolinium – i.e. all lesions are acute monophasic)

Blood - platelet counts↑, ESR mildly elevated (greater elevation suggests vasculitis or infection).

EEG - widespread slowing of background rhythms.

TREATMENT

a) IV METHYLPREDNISOLONE 20 mg/kg/d (maximum 1 g/d) for 3-5 days → oral taper for 3 weeks
   - improvement usually requires several days.

b) IVIg 2 g/kg for 2-3 days - preferable when meningo-encephalitis cannot be excluded.

c) **plasma exchange** for severe deficits and little response to corticosteroids.

PROGNOSIS

- mortality < 2% (esp. *measles-associated ADEM*).
  - 50-90% survivors have **marked recovery** (complete recovery may be observed even in children who become blind, comatose, and quadriparetic).
    risk factors for bad recovery: age < 2 yrs, transverse myelitis.
  - long-term (10-y follow-up) ***risk for development of MS*** - 25%.

ACUTE NECROTIZING HEMORRHAGIC ENCEPHALOMYELITIS (ANHEM), s. Acute Hemorrhagic Leukoencephalitis of WESTON HURST

- hyperacute variant of ADEM.

- affects mainly children and young adults.
- almost invariably preceded by recent episode of *upper respiratory infection*.
- immunopathogenesis similar to ADEM (immune sensitization to MBP).
- macroscopy - brain is swollen, with bilateral ***petechial hemorrhages*** throughout white matter (hemispheres, brainstem, and spinal cord).
- microscopy ≈ hyperacute EAE with **perivenous demyelination and intense infiltration** by mononuclear and especially polymorphonuclear cells!
- necrosis of walls of venules → fibrin deposition, petechiae, disseminated necrosis of white and gray matter.
- coalescence of smaller lesions → large necrotic foci.

CLINICAL FEATURES

- sudden headache → fever, various focal signs (esp. seizures, quadriplegia) → rapid progression (few hours to several days) from lethargy to coma.
- > 80% cases are fatal (within 2-4 days).

DIAGNOSIS

- **CT** – brain edema, diffuse areas of hypodensity in white matter.
- late **MRI** – evidence of blood products.
- **blood** – marked ***leukocytosis***, ESR↑.
- **CSF**:
  1) marked ***pleocytosis*** up to 3000 cells/mm^3 (preponderance of POLYMORPHONUCLEARS!)
  2) evidence of hemorrhage
  3) total protein↑.

THERAPY

- supportive + METHYLPREDNISOLONE-PREDNISONE regimens.

BIBLIOGRAPHY for ch. "Demyelinating Disorders" → follow this LINK >>