

# 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

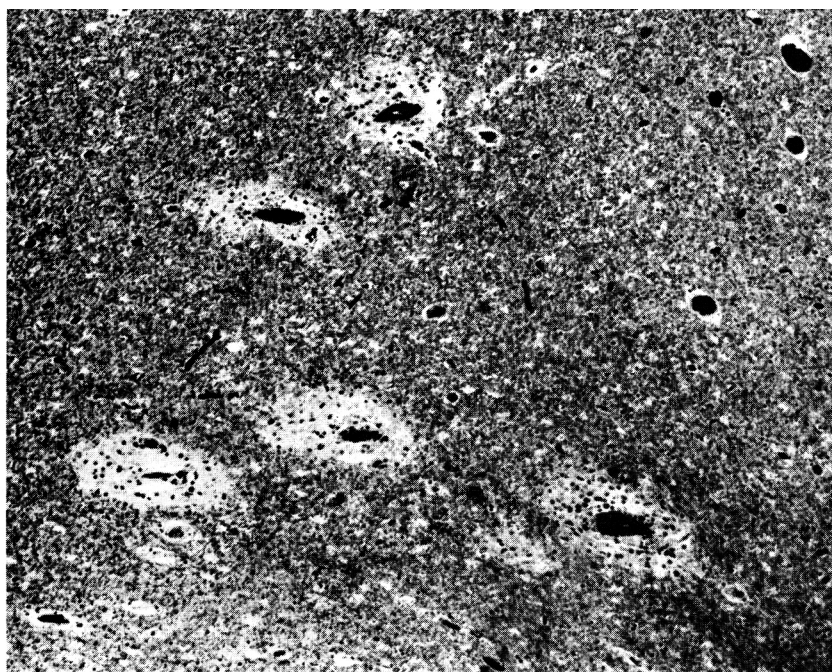
- **transient cell-mediated autoimmune response toward myelin** (e.g. myelin basic protein).

- 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) (Wolcke stain).

### ETIOLOGY

- 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.
- 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 1<sup>st</sup> decade, < 20% - during 2<sup>nd</sup> 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<sup>3</sup>.

**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

- IV **METHYLPREDNISOLONE** 20 mg/kg/d (maximum 1 g/d) for 3-5 days → oral taper for 3 weeks
  - improvement usually requires several days.
- IVIg** 2 g/kg for 2-3 days - preferable when meningo-encephalitis cannot be excluded.
- 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<sup>3</sup> (preponderance of POLYMORPHONUCLEARS!)
  - 2) evidence of hemorrhage
  - 3) total protein↑.

### THERAPY

- supportive + **METHYLPREDNISOLONE-PREDNISONE** regimens.

BIBLIOGRAPHY for ch. “Demyelinating Disorders” → follow this [LINK >>](#)