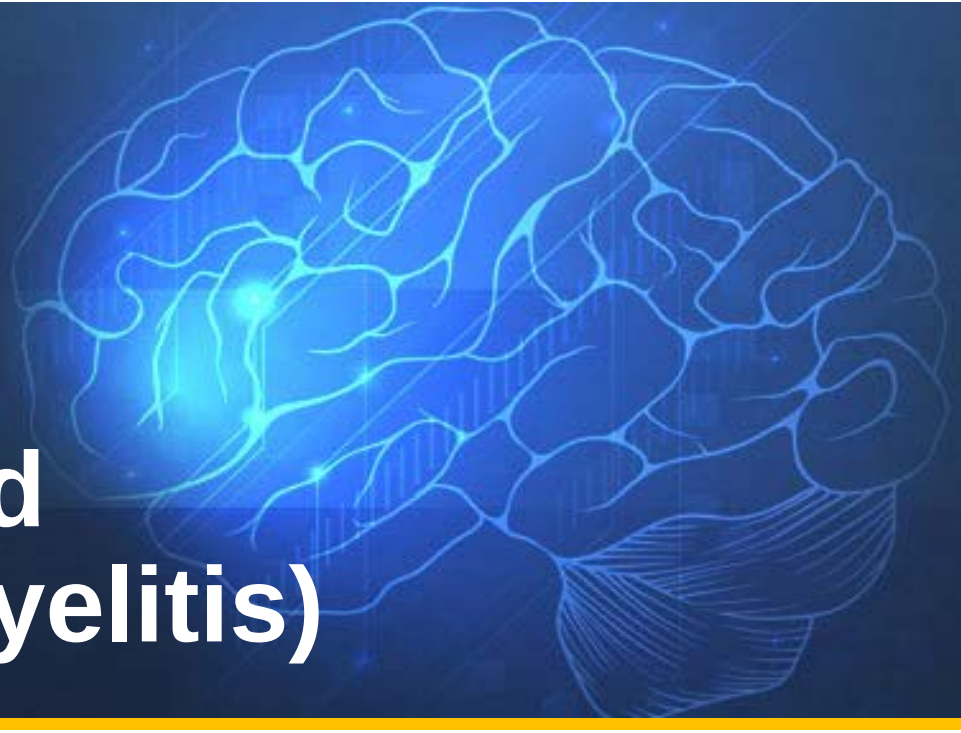
ADEM
(Acute Disseminated Encephalomyelitis)



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SCENARIO… 01

Ms. R. 18/F presented in the emergency with 02 days history of dimness of vision of the right eye followed by left one, with pain on both eyes on movement. In ED she was drowy, confused and irritabile. Her parents states an episodes of cough with fever lasted for 3 days resolved spontaneously 12 days back.

Examination revealed GCS 8 with bilateral optic disc swelling, bilateral planter extensor without neck rigidity. 03 hrs after admission, she developed generalized tonic clonic seizure.

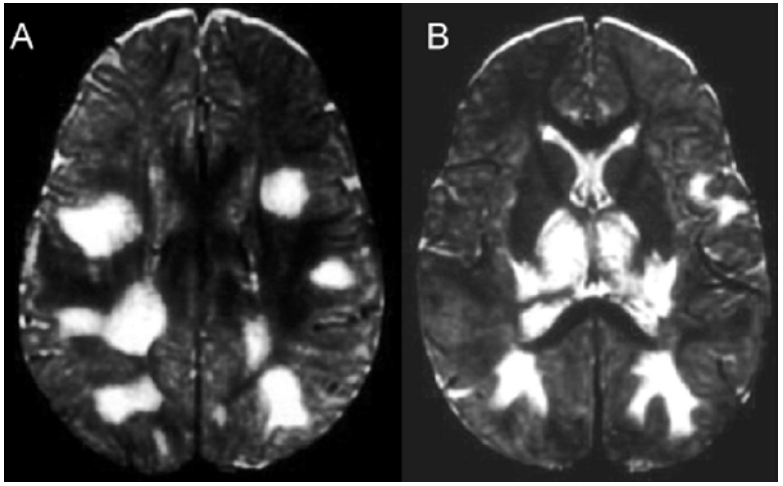
SCENARIO 01 MIMICS

1. Infectious meningitis/encephalitis, viral/bacterial /protozoal / autoimmune
2. Metabolic encephalopathy
3. ADEM
4. NMO
5. Cerebral Venous Sinus Thrombosis

SCENARIO 01 INVESTIGATIONS

1. Blood Biochemistry and Count was normal
2. CSF Study 10 Cells/Cubic mm,
3. Protein & Sugar :Normal
4. AFB & Gram stain: Negative
5. CSF culture: Negative
6. Bacterial Antigen: Negative
7. PCR for Viral: Negative
8. MRI of Head

Dx ??????



SCENARIO… 02

Mr. K. M/24 (old farmer) was licked in his feet by his pet dog. He consulted the nearest Upazilla Health Complex and advised to have anti-rabis vaccination, subcutaneously in peri-umblical region for 14 days.

After 7 injections he developed pain in the back followed by urinary hesitancy progressed to acute retention of urine. He was admitted in Health Complex and 01 day after he developed weakness of both lower limbs with loss of sensations up to Mid Chest. He was conscious, oriented and had total areflexia below umblicous with extensor planter reflex, Loss of all modalities of sensation below nipple and cathether in situ.

SCENARIO 02 MIMICS

1. Acute Transverse Myelitis
2. Other causes of acute myelopathy

3. Investigation : Not Done due to economic condition and facilities
4. Diagnosis: Post vaccinal TM
5. Treatment: IV MP
6. Recovery: Recovered with difficulty in walking

Acute Disseminated Encephalomyelitis (ADEM)

1. **First describing 1724** in patient after smallpox
2. Demyelinating disease of the CNS
   - Monophasic disorder associated
   - Multifocal neurologic symptoms
   - Encephalopathy
   - Bilateral Optic neuritis
3. Usually follows an infection or vaccination.
4. Neuroimaging : Multifocal white matter lesions.
5. Relapse : Uncommon
6. Diagnosis – Clinical, Lack of a distinctive **biological marker**

Epidemiology

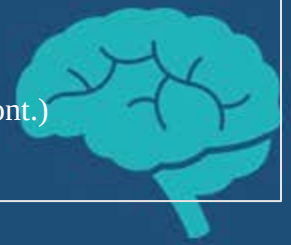
- Annual incidence 0.4–0.8 per 100,000
- Children and young adults, due to high frequency of **exanthemata's** and **other infections** and **vaccination** in this age group.

  Gender : Male predominance.
- Sessional variation
  - **Winter and Spring**

Post-infectious ADEM

- 50-75 % of ADEM- inflammatory attack is preceded by a viral or bacterial infection.
- Measles , Mumps, Rubella
- Varicella zoster, Epstein-Barr, Cytomegalovirus
- Herpes simplex, Hepatitis A, Influenza
- Enterovirus infections.

Post-immunization ADEM (cont.)



- Less than 5 % of ADEM cases follow immunization.
- Rabies, Hepatitis B, Influenza
- Japanese B encephalitis
- Diphtheria /Pertussis / Tetanus
- Measles, Mumps , Rubella,
- Pneumococcus, Polio, Smallpox, and Varicella.

Do all ADEM are monophasic??

Recurrent ADEM

- Subsequent attack with same symptoms occurred during the initial attack.
- The MRI: similar to the initial attack, no lesions, but there could be an enlargement of the lesions from the original episode

Do all ADEM are monophasic??

Multiphasic ADEM

*New areas of the central nervous system from the initial or previous attacks.

*Signs of encephalopathy, but symptoms and neuroimaging findings are in different areas from the initial attack.

*Might be new lesions evident on MRI, might also be evidence of partial or complete resolution of the lesions associated with the first episode

ADEM MIMICS and CONTROVERSICS/ OHER DEMYELINATING DISEASE

ADEM

- Monophasic
- Recurrent
- Multiphasic

- Multiple Sclerosis
- Clinically isolated syndrome
- NMO spectrum disorders

SPECTRUM OF ADEM

1. **Acute disseminated encephalomyelitis**
   - Postinfectious.
   - Postvaccinial.
2. **Acute haemorrhagic leucoencephalitis**
3. **Restricted form of ADEM**
   - Transverse myelitis.
   - Optic neuritis.
   - Cerebellitis.
   - Brain stem encephalitis.
4. **Multiphasic form of acute disseminated** encephalomyelitis and multiple sclerosis

PATHOLOGY : ADEM

- **Pathological hallmark** - areas of peri-venous demyelination, infiltration of lymphocytes and macrophages.
- Other changes - hyperemia, endothelial swelling, and vessel wall invasion by inflammatory cells, perivascular edema, and haemorrhage.
- Present in the small blood vessels of both white and grey matter.
- **Post infectious encephalomyelitis** typically involves the white matter, lesions in grey matter can also been seen.

CONTROVERCIES & MIMICS OF PATHOLOGICAL FEATURES

Feature	ADEM	Acute multiple sclerosis	Acute haemorrhagic leucoencephalitis	Neuromy-elitis optica
Perivascular infiltrates				
1. Lymphocytes	++	++	++	++
2. Macrophages or monocytes	++	++	++	++
3. Polymorphs	--	--	++	++
4. Eosinophils	--	--	--	++
Perivascular haemorrhage	--	--	++	--
Necrotising venules	--	--	++	+
Perivascular demyelination	±	±	++	++
Axonal damage	±	±	++	++

HALLMARK **PERIVENULAR LYMPHOCYTIC INFILTRATE WITHOUT HEMORRAGE OR NECROSIS**

PATHOPHYSIOLOGY : ADEM

- ADEM - transient autoimmune response against myelin or other autoantigens, possibly, via
  - **molecular mimicry**
  - non-specific activation of an autoreactive T cell clone.
  - Genetic susceptibility
- Human leucocyte antigen class II genes have the most significant influence.
- Immunopathological events
  - Initial T cell priming and activation
  - Subsequent recruitment and effector phase

SIGNS & SYMPTOMS

- The neurological signs from the inflammatory attack often begin with:

  Fever, Headache, and Vomiting

* Encephalopathy is a characteristic feature of ADEM and usually develops rapidly.

SIGNS & SYMPTOMS

Encephalopathy results in symptoms, such as:

- Altered level of consciousness (lethargy →coma)
- Acute cognitive dysfunction
- Behavioral changes
- Seizures

In about ⅓ of those diagnosed.

SIGNS & SYMPTOMS

Other common neurologic signs of ADEM include:

- Long tract pyramidal signs
- Acute hemiparesis
- Cerebellar ataxia
- Cranial neuropathies
- Optic neuritis- Bilateral

SIGNS & SYMPTOMS

- Peripheral nervous system (PNS) involvement 43 %
  - Demyelinating and Subclinical.
- Most adult patients present clinically in a similar fashion with headache, fever and meningismus, and a higher frequency of sensory deficits.
- Optic neuritis is infrequent in adult ADEM.
- Restricted forms : ON, Transverse myelitis, Cerebellitis, Brain stem encephalitis.

ACUTE DISSEMINATED ENCEPHALOMYELITIS: CLINICAL SYNDROMES

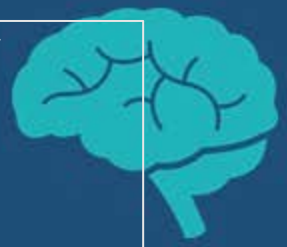
1. **Most common-polysymptomatic presentation**
2. **Site restricted syndromes**
    - Acute cerebellar ataxia
    - Transverse myelitis
    - Brainstem syndromes
    - Optic neuritis (bilateral)
    - Myeloradiculitis

DIAGNOSIS CLINICAL

- ADEM : develop multifocal neurologic abnormalities with:
  - Confusion
  - Excessive irritability
  - Altered level of consciousness (encephalopathy)

Especially if the onset of symptoms occurs within 1 to 2 weeks after a viral/bacterial infection or a vaccination

Clinical characteristics of patients initially diagnosed with ADEM (Retrospective Multicenter US Study)



CLINICAL PRESENTATION	NO (%)	CLINICAL PRESENTATION	NO (%)
Preceding event	131 (58)	Seizures	36 (16)
Polyfocal onset	220 (97)	Weakness	115 (51)
Encephalopathy	137 (61)	Ataxia	80 (35)
Headache	120 (53)	Gait abnormality	126 (56)
Nausea/vomiting	86 (38)	Optic neuritis	24 (11)
Fever	90 (40)	Other cranial nerve palsies	82 (36)
Sensory abnormalities	60 (27)	Meningismus	24 (11)

CLINICAL FEATURES OF ADEM & MIMICS- DIFFENTIAL DIAGNOSIS

Clinical Presentation	Differential Diagnosis & Mimics
Meningeal signs or headache	Encephalitis/Meningitis, systemic autoimmune disorders (e.g., neurosarcoidosis, SLE), CNS vasculitis, CVT
Stroke-like events	CNS vasculitis, anti-ph ab antibody syndrome, mitochondrial diseases (MELAS, POLG-related disorders)
Recurrent seizures	Infectious or autoimmune encephalitis, CVT, PRES
Dystonia/parkinsonism	Infectious or autoimmune encephalitis
Neuropsychiatric	SLE, autoimmune encephalitis
Encephalopathic events (Recurent)	Genetic/metabolic disorders, SLE, autoimmune encephalitis, ANE
Optic Neuritis	NMO, SLE, CVT, MS

CSF STUDY : ADEM & MIMICS

1. Routine Blood Examination: often normal

- **Cerebrospinal fluid-** Cell count >50/mm3 or neutrophilic predominance or protein >100 mg/dL
  - Increased amounts of gamma globulin and IgG and raised levels of myelin basic protein.
  - Glucose usually normal.
  - Oligoclonal band rare. IgG - demonstrated-58% of adult and 29% of pediatric cases

CSF mimics and controversies: Differential Diagnosis

Meningitis & Encephalitis , MS,CIS,NMOSD, Connective tissue disorders, SLE

ELECTROENCEPHALOGRAPHY : ADEM & MIMICS

Abnormalities are common but are non-specific.

- Mild generalized slowing,
- Severe generalized slowing with infrequent focal slowing and epileptiform discharges.

Mimics & Controversies :

Metabolic encephalopathy, Epilepsy, Generalized and LRE, Non convulsive status

INVESTIGATIONS: ADEM

4. Neuroimaging-

Computed tomography-

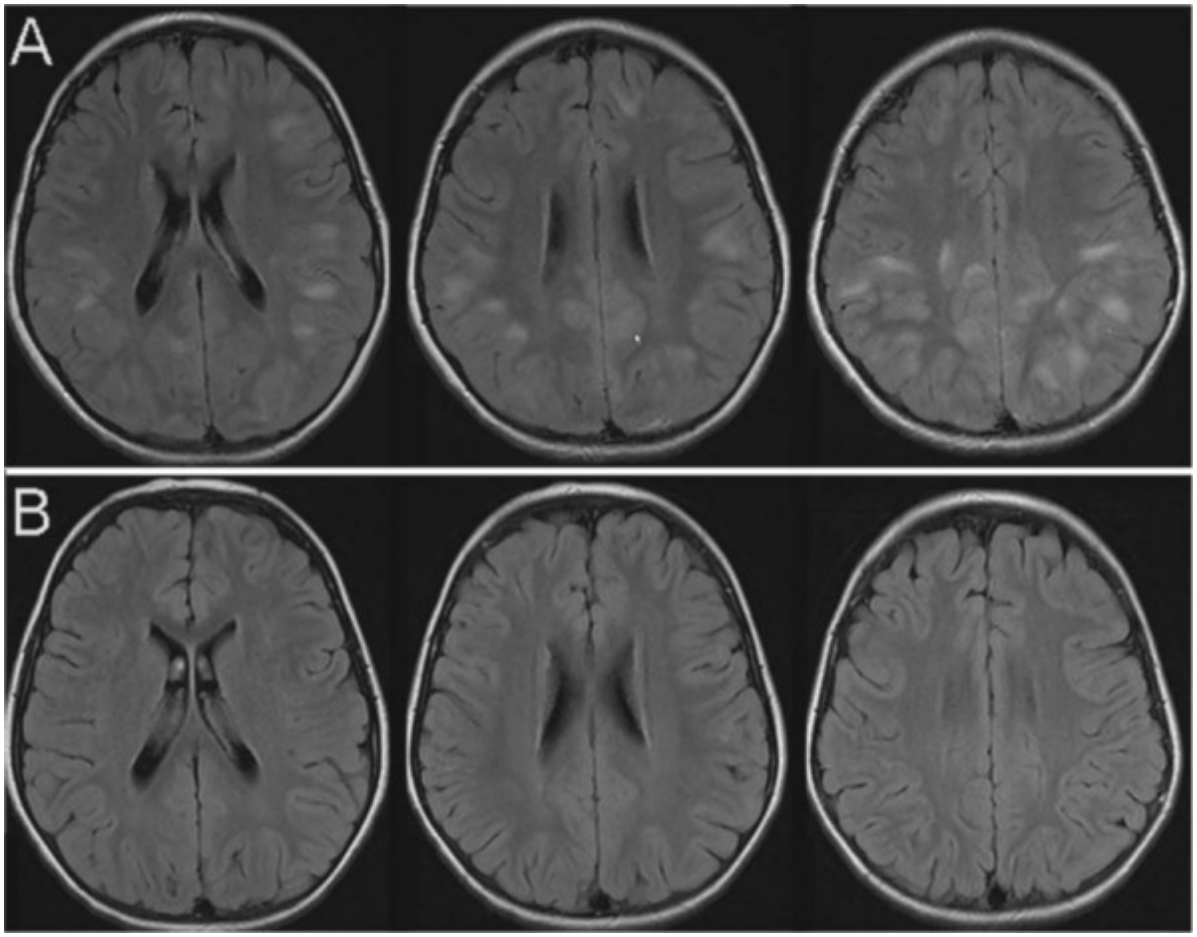
- Normal at onset and usually becomes abnormal 5–14 days later.
- Typical computed tomographic appearance is that of low attenuation, multifocal lesions in the subcortical white matter.

INVESTIGATIONS: ADEM

5. MRI

- Large, multiple, bilateral but asymmetric, poorly demarcated, areas of increased signal on T2-weighted and FLAIR sequences which can affect both white and gray matter
- Gray matter involvement can be neocortical or deep gray matter (thalamus, basal ganglia).
- Brainstem and cerebellum are commonly involved.
- Associated edema, swelling and localized mass effect can be seen in larger lesions.
- Enhancement is not commonly encountered (10–30%), can be marginal and/or nodular in distribution.

INVESTIGATIONS: ADEM MRI



(A)

1. Typical poorly demarcated lesions with white matter and grey matter.
2. No contrast enhancement .

(B)

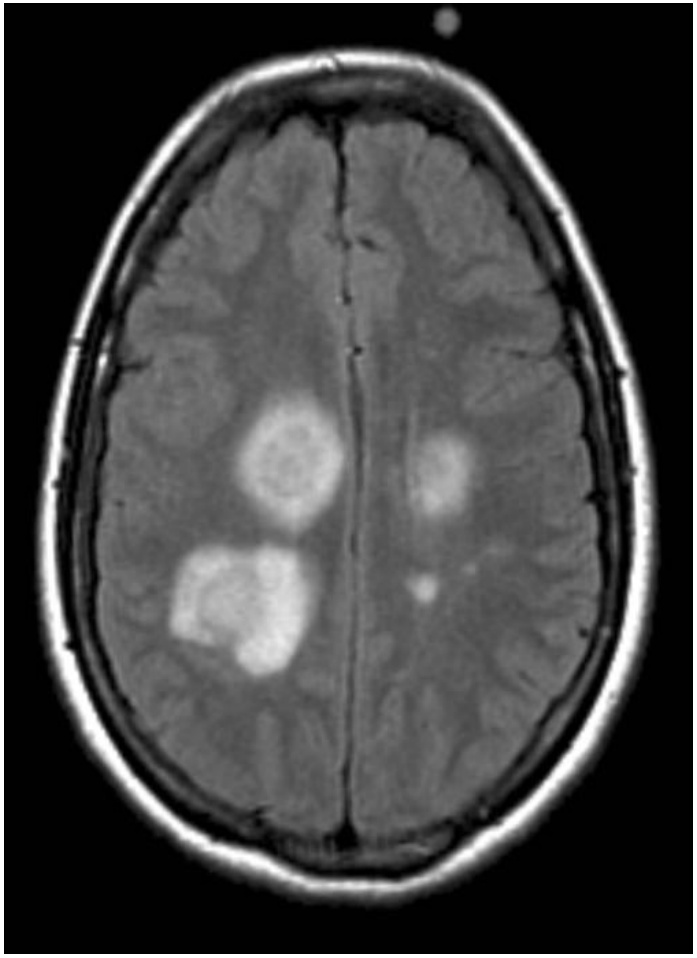
Follow up Image (03 Months Later)

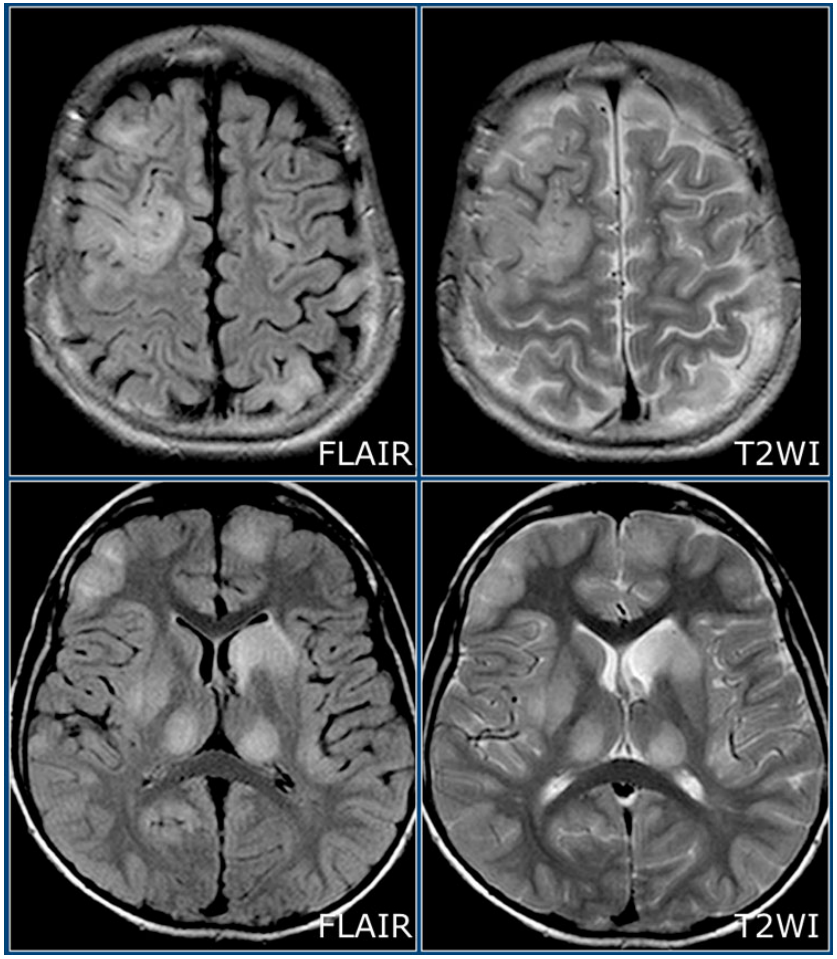
No residual change

INVESTIGATIONS: ADEM MRI

Axial T2-weighted FLAIR MRI of the brain in a child with acute disseminated encephalomyelitis (ADEM).

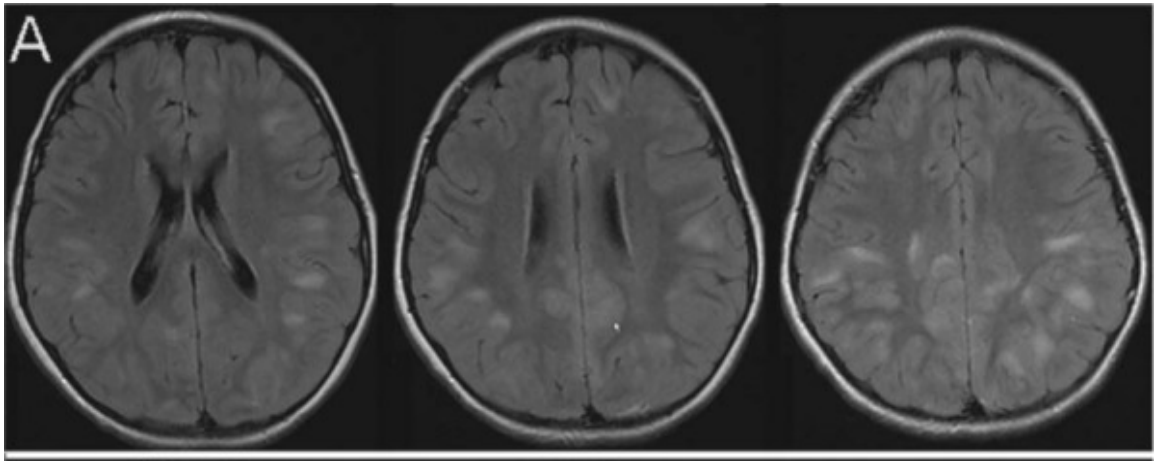
INVESTIGATIONS: ADEM MRI





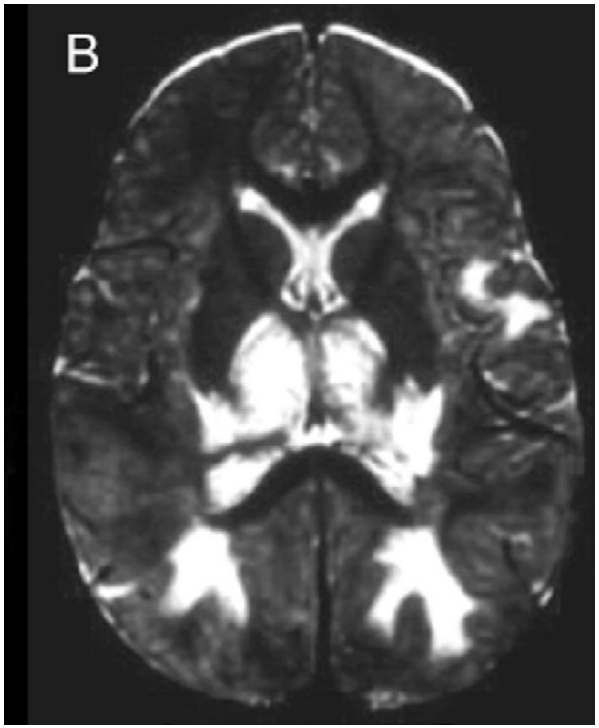
MRI PATTERN: D/D & MIMICS
Multifocal white matter lesions

- Multiple sclerosis, Primary CNS vasculitis, Secondary CNS vasculitis (e.g., CNS lupus, Behçet disease), Neurosarcoidosis, Hashimoto encephalopathy (SREAT), Mitochondrial; POLG-related disorders, Posterior reversible encephalopathy syndrome



MRI PATTERN: D/D & MIMICS
BITHALAMIC OR BISTRIATAL LESIONS

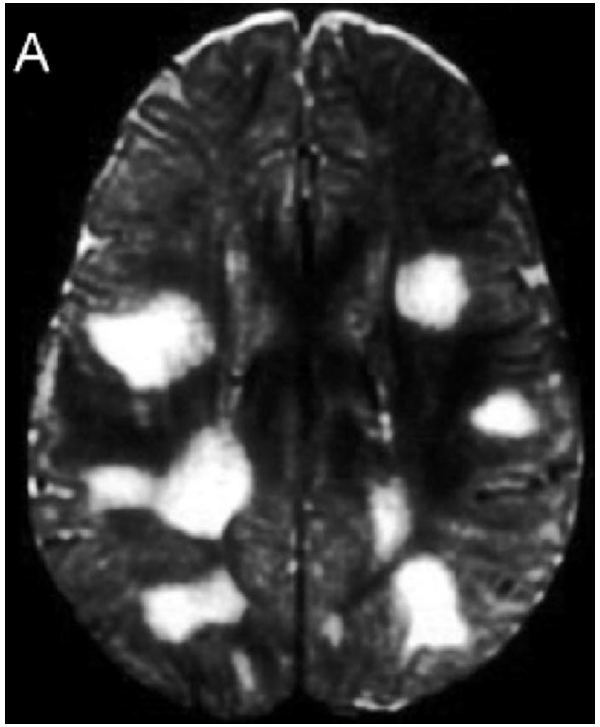
- Acute necrotizing encephalopathy, Biotin-thiamine-responsive basal ganglia disease Mitochondrial, Deep cerebral vein thrombosis
- Japanese encephalitis/other encephalistis, Extrapontine myelinolysis, Bithalamic glioma



MRI PATTERN: D/D & MIMICS

Bilateral and diffuse large white matter lesions

- Leukodystrophies, Toxic leukoencephalopathies, Hemophagocytic lymphohistiocytosis, Gliomatosis cerebri



Tumefactive lesions

- Astrocytoma, Lymphoma
- Abscess/infection

ADVANCED NEUROIMAGING TECHNIQUES

- MRS
- Diffusion tensor imaging (DTI)
- Magnetic transfer imaging (MTI)
- Magnetization transfer and diffusion tensor MR imaging
- Double inversion recovery improve detection of cortical lesions.

MANAGEMENT of ADEM

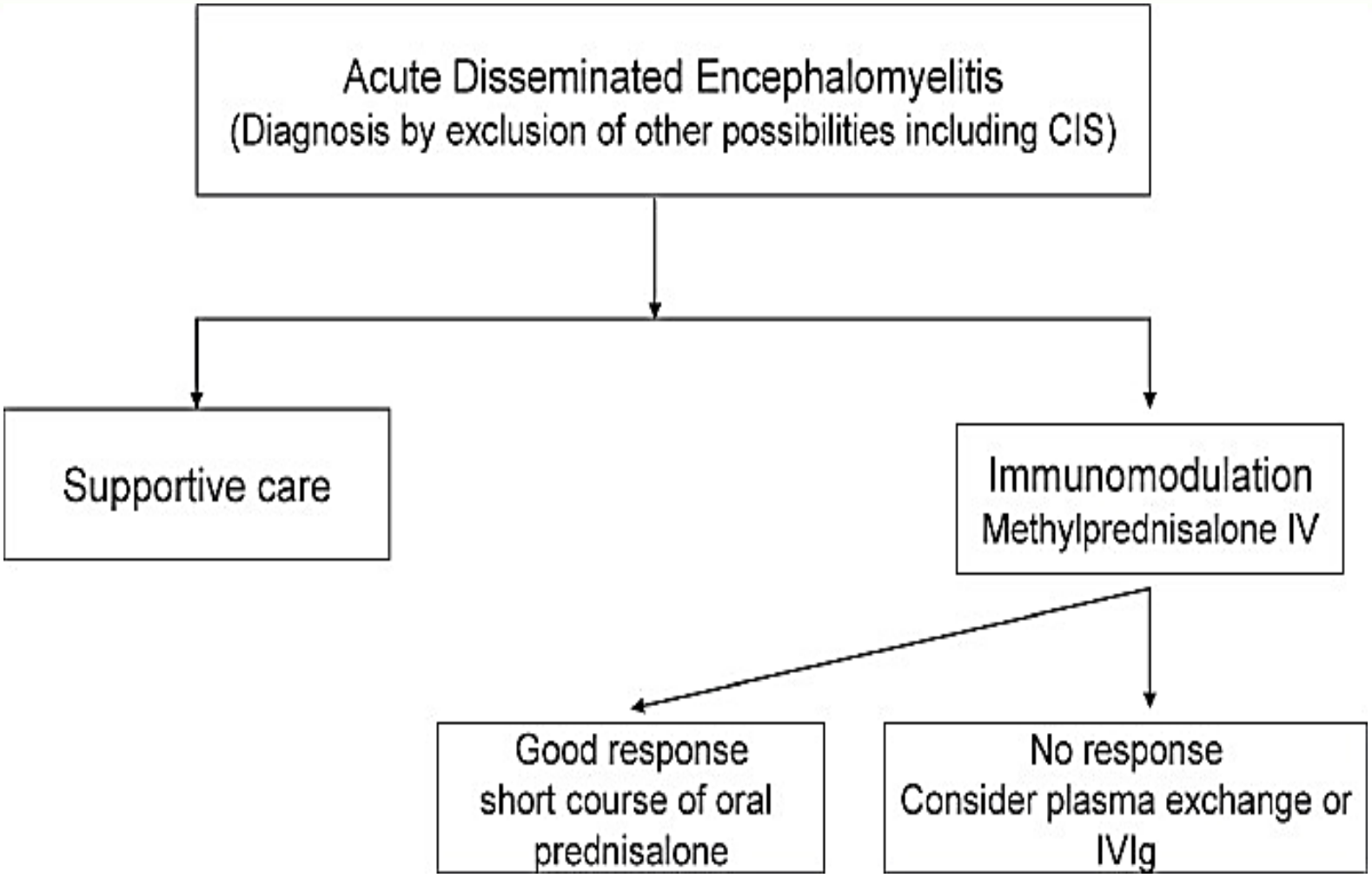
1. SUPPORTIVE
2. **Specific**—high-dose intravenous methyl prednisolone, intravenous immunoglobulin (IVIg), and plasma paresis, and
3. Physical and rehabilitation therapy

MANAGEMENT of ADEM

Supportive Care

- Airway protection: Altered mental status, mechanical ventilation
- Anti-seizure medication: Levetiracetam, Phenytoin, Midazolam, Diazepam, Lorazepam
- Fluid and electrolyte balance
- Nutrition
- Prophylactic anticoagulation for DVT

MANAGEMENT of ADEM



ACUTE TREATMENTS
Practice Guideline

- First consider a treatment with antibiotics and/or acyclovir until an infectious cause is ruled out

*A high dose of intravenous corticosteroids, for 3-5 days is the primary and most common first treatment of ADEM

*Corticosteroids can be used concurrently with antibiotics and acyclovir

MANAGEMENT of ADEM (SPECIFIC)

- **Immunomodulation-**

Methyl Prednisolone-

- Intravenous methyl prednisolone (10–30 mg/kg/day, up to a maximum of 1 g/day) for 3–5 days .
- Full recovery 50%–80% of patients.
- Oral corticosteroid continued with gradual tapering over 6 weeks to reduce the risk of relapses.
- Avoid any type of vaccination for first 6 months following recovery.

- **Dexamethasone**
- 1mg/kg for 3 to 5 days followed by oral steroid taper for 4 to 6 weeks

MANAGEMENT of ADEM (SPECIFIC)

Intravenous immunoglobulin (IVIg)-

- 0.4 gm/kg/day for 5 days
- second-line treatment, when corticosteroids fail.

Plasma exchange (PE)-

- Course of 4–6 PEs have been shown to be associated with moderate to marked and sustained improvement.
- Predictors associated with improvement include male sex, preserved reflexes, and early initiation of treatment

MANAGEMENT of ADEM (SPECIFIC)

- **Choice of second-line treatment**
  - Individualized
  - Severity of the disease
  - Complications
  - Comorbidities.
- IVIg more effective in patients with peripheral nervous system involvement
- PE in patients with tumefactive demyelination.
- Cyclophosphamide and hypothermia have been used with success in patients with fulminant ADEM.

PROGNOSIS

- Long-term prognosis depends on the etiology.
- Postmeasles patients: higher mortality rate , significant morbidity
- Nonmeasles cases : favorable ,full recovery 50%–75% of patients, in 1–6 months of follow up.
- Common sequelae: focal motor deficits, mild ataxia to hemiparesis.

Indicators for poor prognosis

Hyperacute onset: severe neurologic deficits, aggressive disease, and unresponsiveness to steroids

LONG-TERM CARE

- Long-term clinical follow-up and sequential imaging by MRI are normally required to confirm a diagnosis of ADEM.

*Relapse with new lesions, not compatible with a diagnosis of monophasic ADEM

Final diagnosis of patients initially diagnosed with ADEM

FINAL DIAGNOSES	No. (%)
Monophasic ADEMa	156 (68)
MS	24 (11)
Multiphasic ADEM	23 (10)
NMOSD	8 (4)
Susac syndrome	2 (1)
Lupus cerebritis	2 (1)
CNS lymphoma	2 (1)
Astrocytoma grade	3 anaplastic 1
Primary brain tumor	1
CNS Lyme disease	1
CLIPPERS	1
Mitochondrial disorder involving the CNS	1
Glioblastoma multiforme	1
PANS/autoimmune encephalitis	1
CNS vasculitis	1
Rabies myeloencephalitis	1

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