ACUTE ENCEPHALITIS &ENCEPHALOPATHY

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DEFINITIONS

- *Encephalopathy:* Clinical syndrome of altered mental status, manifesting as reduced consciousness or altered behaviour

- *Encephalitis*: An inflammatory process of the brain parenchyma

Acute encephalitis syndrome

- A person of any age, presenting at any time of year, with acute onset of fever and altered mental status manifesting with symptoms such as confusion, disorientation, coma, or inability to talk and/or new onset of seizures (excluding simple febrile seizures)

WHO. Acute encephalitis syndrome. Japanese encephalitis surveillance standards. January 2006. from WHO recommended standards of surveillance of vaccine preventable diseases

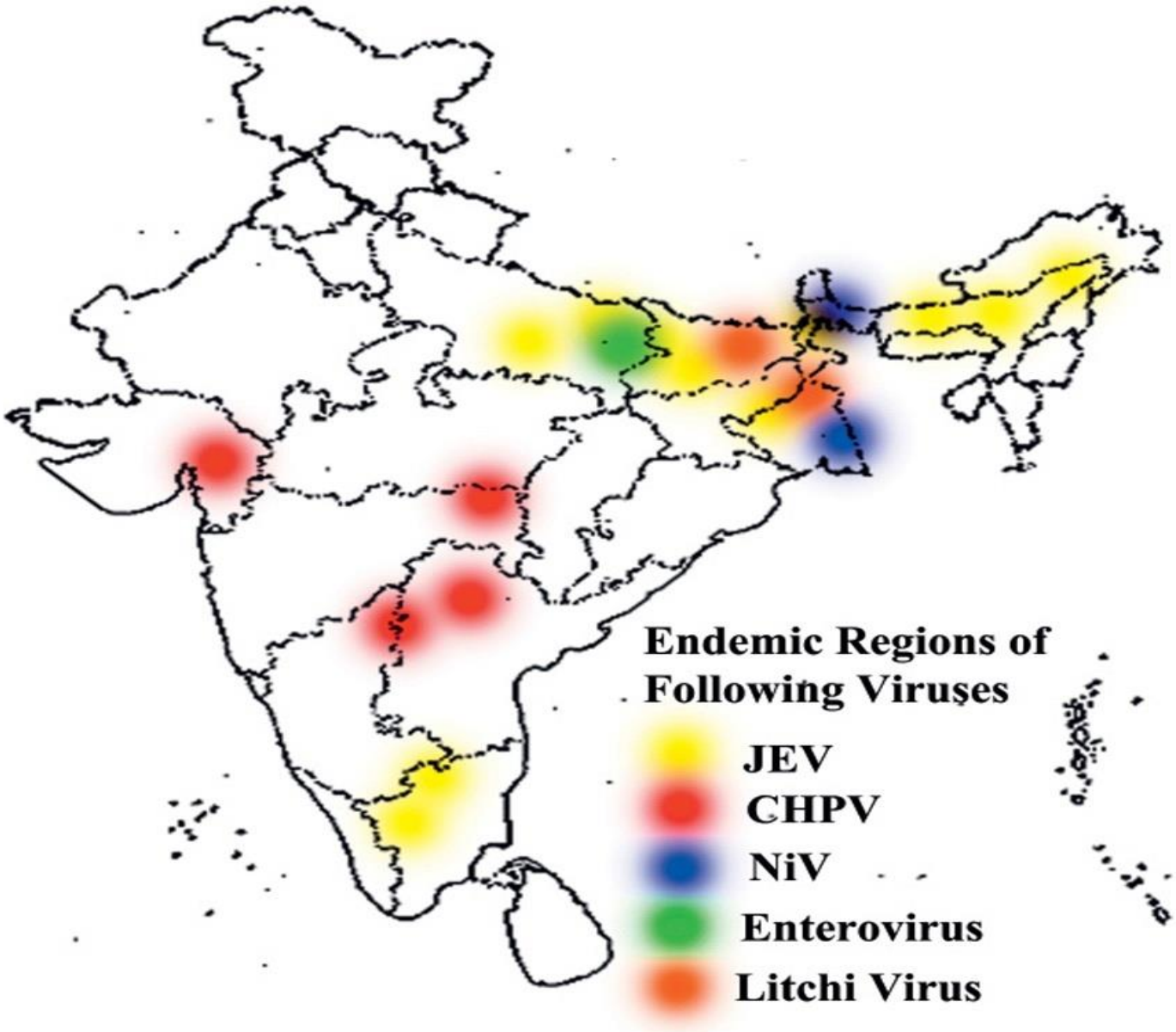
ETIOLOGY
VIRAL

Epidemic

- Japanese Encephalitis
- Enterovirus
- West Nile
- Nipah virus
- Dengue virus
- Chandipura
- Chikungunya

Sporadic

- HSV-1
- EBV
- Varicella zoster
- HIV
- Human herpes virus-6
- Measles
- Mumps
- Kyasanur forest virus


Endemic Regions of
Following Viruses
JEV
CHPV
NiV
Enterovirus
Litchi Virus

Other causes

- Bacterial: TB, Rickettsia, Leptospira
- Protozoal: Malaria, Toxoplasma
- Poisoning: Lead, Cassia, Litchi
- Autoimmune – ADEM, anti NMDA encephalitis
- Metabolic

Toxins

- AES outbreaks in north and eastern India linked to children eating unripe litchi fruit on empty stomach.
- Litchi seed contains toxins hypoglycin A and methylene cyclopropyl glycine (MCPG), cause vomiting, sudden high fever and seizures
- If ingested in large quantities requiring hospitalisation in young, severely malnourished children.

Evaluation and management

- Step I: Rapid assessment and stabilization
- Step II: Clinical evaluation: History and Examination
- Step III: Investigation/Samples to be collected
- Step IV: Empirical Treatment
- Step V: Supportive care and treatment
- Step VI: Prevention/treatment of complications and rehabilitation

Step I: Rapid assessment and stabilization

- Establish and maintain airway
- Ventilation, Oxygenation
- Circulation
- Identify signs of cerebral herniation or raised ICP.
- Temperature: treat fever and hypothermia
- Treat ongoing seizures- Benzodiazepine, followed by phenytoin loading

Step II: Clinical evaluation: History and Examination

- There may be a prodrome of upper respiratory illness, flu-like illness or diarrhea.
- Altered behavior, cognition, personality changes, altered consciousness.
- History of recurrent episodes of encephalopathy.
- Family history of previous infant/child deaths.
- Recent history of travel

Etiological Clues

- Pallor : Cerebral malaria, or IC bleed
- Icterus : Leptospirosis, hepatic encephalopathy, or cerebral malaria.
- Skin rashes : Dengue, Measles, Varicella, Rickettsial diseases
- Petechiae : Dengue and viral hemorrhagic fevers
- Parotid swelling and orchitis : Mumps

Clues…

- Limb weakness: Enterovirus, Poliomyelitis, ADEM
- Myoclonic jerks : Enterovirus encephalitis
- Dystonias : Japanese B encephalitis.
- Orofacial dyskinesias & psychiatric features such as delusions, hallucinations and catatonia are characteristic of anti-NMDA receptor encephalitis

Examination

- GCS
- Pupillary size, shape, symmetry and response to light: brainstem and third nerve dysfunction.
- Trunk, limb movements, position, focal deficits
- Posturing : brainstem herniation syndrome.
- Fundus examination: papilledema & retinal hmg
- Systemic examination: HSM, pulmonary involvement, myocarditis

Step III: Investigation

- Basic investigations : CBC, RFT, Electrolytes, LFT, Blood Culture, CXR
- Lumbar puncture, C/I:
  - Hemodynamically unstable
  - Features of raised ICT
  - Platelets count < 50000
  - Local site infection
- Neuroimaging: should be done before LP if the patient is unstable or has features of raised ICT
  - Presence of bleed, cerebral edema, clue towards etiology, etc

Microbiological investigations in AES

Virus	Sample and test	Comment
JE	IgM capture ELISA in CSF/Serum	Further confirmatory tests needed •Cross reaction with flaviviruses (dengue) • Vaccination
Enterovirus	RT-PCR in CSF Virus isolation from serum, stool, throat swab	Highly specific
Dengue	IgM capture ELISA in CSF	CSF positivity is diagnostic of dengue encephalitis
HSV	•DNA PCR in CSF •HSV specific Abs	•For duration< 12d- DNA PCR (Sn> 95%, Sp- 100%) •>12 days- IgG Abs preferred if DNA PCR not done or neg

Microbiological investigations in AES

Virus	Sample and test	Comment
Mumps	RNA PCR in CSF	Sn> 95%
Varicella	DNA PCR in CSF	-
Nipah	IgM capture ELISA inCSF/Serum PCR in CSF	Sn: serum- 70% CSF- <1/3rd of patients
Measles	IgM in CSF	High false positives
Chandipura	IgM in CSF PCR in CSF	-

Sharma et al. IAP. Expert group opinion on encephalitis. Consensus guidelines on evaluation and management of suspected acute viral encephalitis in children in India. 2012

Other investigations

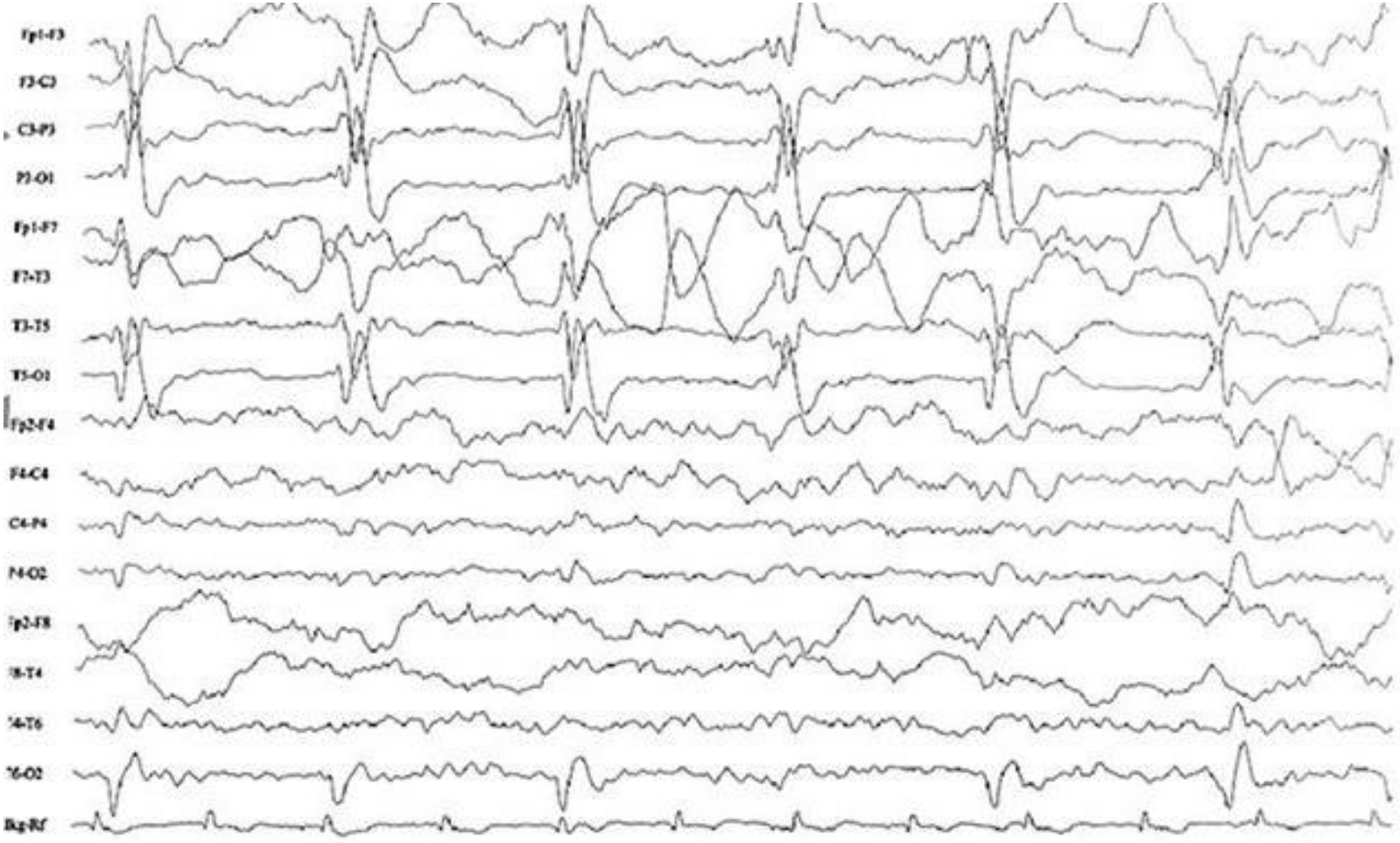
- Other microbiological investigations: These samples include urine, throat swab, nasopharyngeal aspirate, swab from vesicles or rash, if present.
- Unexplained encephalopathy with fever and rash : Weil- Felix test, rickettsial serology
- Unexplained encephalitis : HIV testing

Guidelines for collection, storage and transport of samples in unexplained epidemic of AES

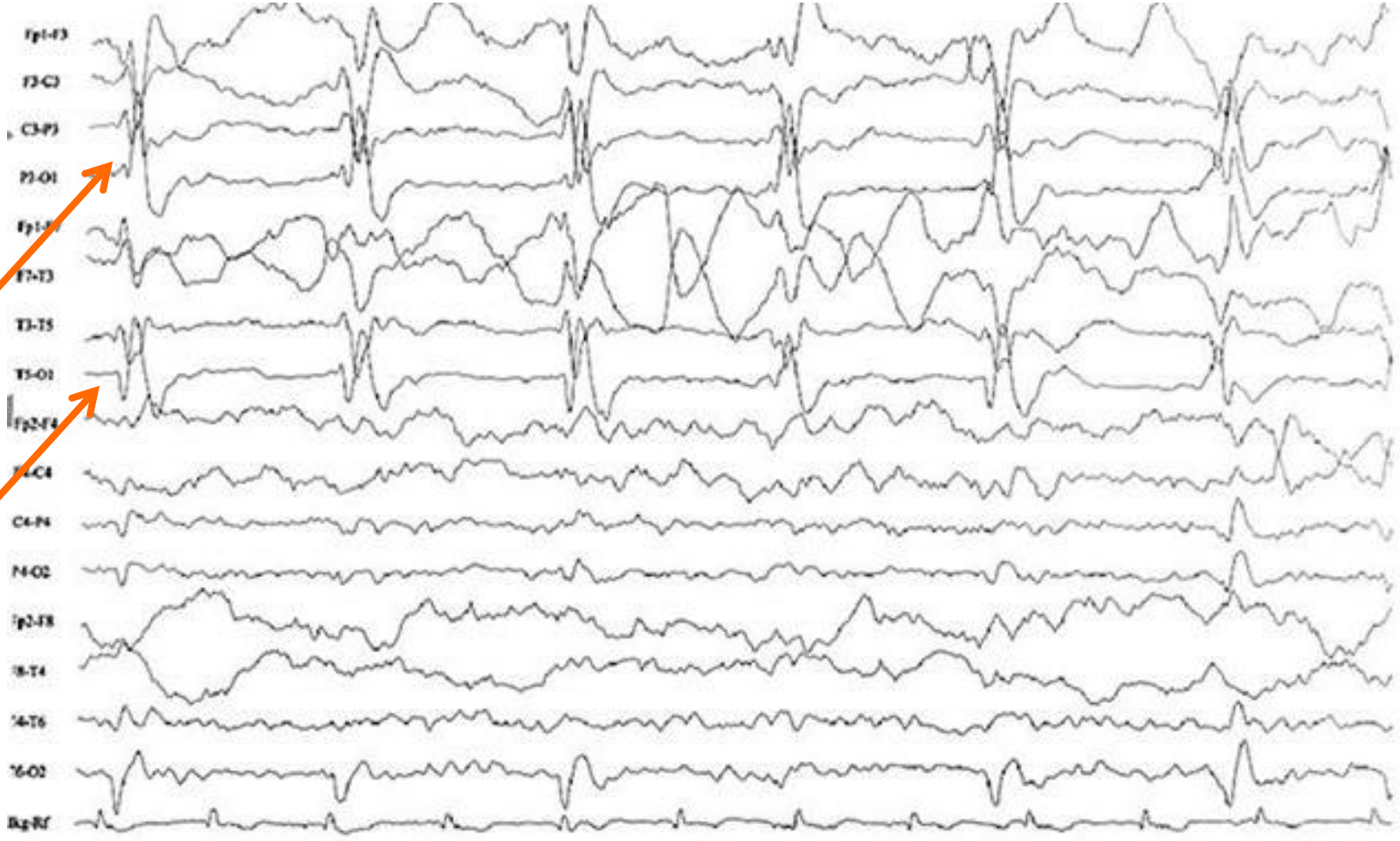
Sample	Guidelines
Blood	• Within 4 days after the onset for isolation & at least 5 days after onset of illness for detection of IgM AB • A 2nd convalescent sample: at least 10-14 days after 1st sample for serology • Serum should be shipped on wet ice within 48 hours or stored for max 7 days
CSF	• Cytology, bacteriology, biochemistry and virology- PCR, serology; storage @ +4°C; delays: -80°C
Swab	Dacron/nylon swabs; in a virus transport medium
Urine	10-20 ml; in a sterile container for mumps virus culture and PCR; store at -20°C
Stool	For enterovirus culture, in clean containers; store at -20°C
Brain biopsy	• Specimens: Unfixed into a sterile container; smears: viral Ag detection by IF AB staining and for EM with neg stain • Emulsified brain tissue: tissue culture and PCR(after protienase K treatment)

Investigations…

- EEG is not routinely needed. It must be performed in children with unexplained altered sensorium to look for suspected non-convulsive status epilepticus.
  - PLED in HSV encephalitis
  - Extreme delta brush in autoimmune encephalitis
- Autoimmune encephalitis panel – anti-NMDAR, VGKC Ab in CSF
- Metabolic work up in cases of recurrent bouts of encephalopathy/ premorbid developmental delay


Fp1-F3
F3-C3
C3-P3
P3-O1
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp2-F8
T4-T6
T6-O2

PLEDs in EEG: HSV encephalitis



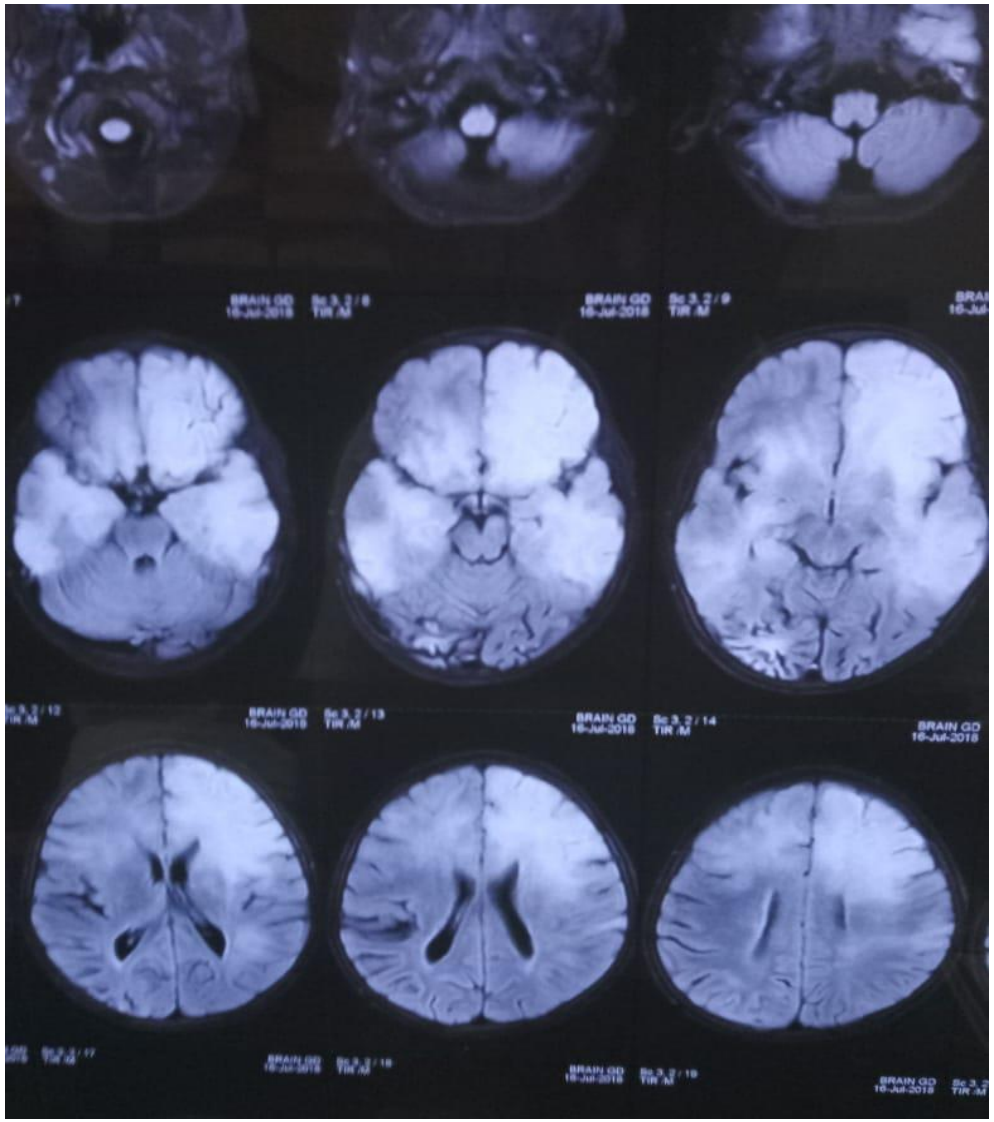
MRI Brain findings in some viral encephalitis

Etiology	MRI finding
HSV	Abnormal signal intensity in medial temporal lobe, cingulate gyrus and orbital surface of frontal lobes
JEV	Abnormal signal intensity in thalami, substantia nigra , basal ganglia
EV 71	Abnormal signal intensity in the dorsal pons, medulla, midbrain, dentate nuclei of the cerebellum,
Chandipura	Normal
Nipah virus	Focal subcortical & deep white and gray matter lesions in pons, white matter, cortex, associated cerebellitis, vasculitis, vasculopathy

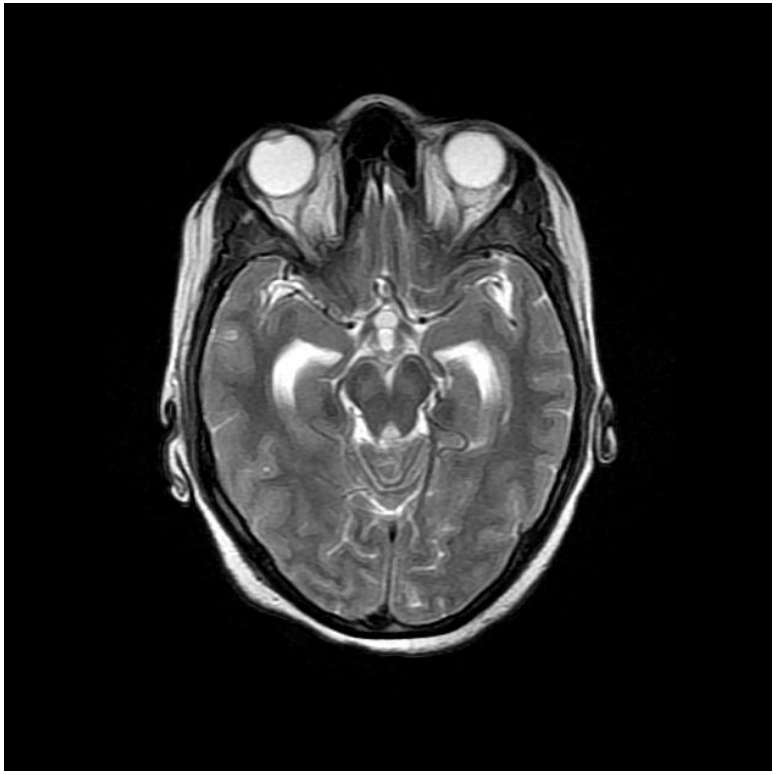
MRI Brain findings

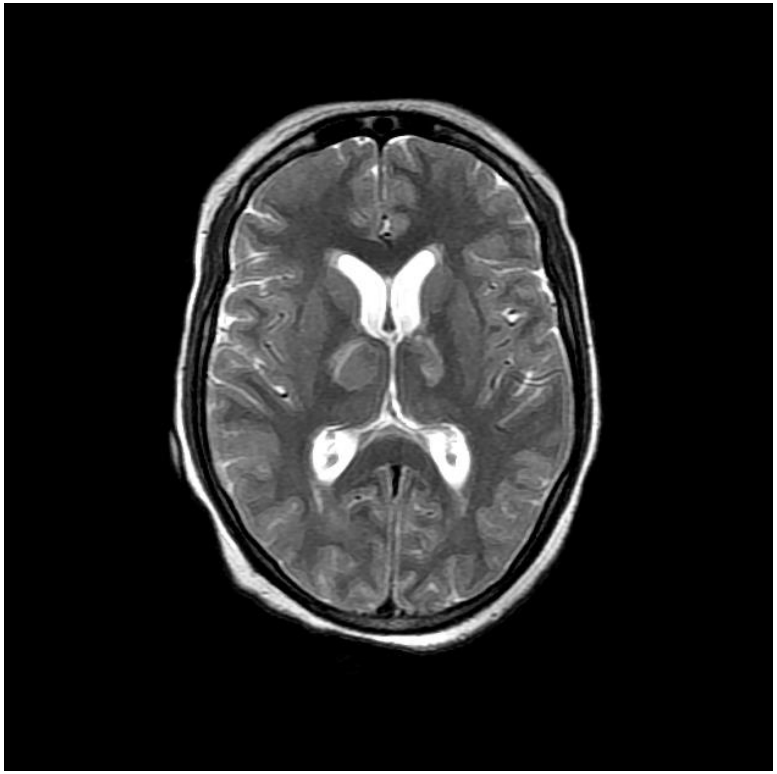
Etiology	MRI finding
Varicella	Multifocal abnormalities in cortex, cerebellitis, vasculitis, vasculopathy
West Nile	Abnormalities in deep gray matter and brainstem
Dengue virus	Mostly MRI is normal/edema/scattered focal lesions
ADEM	Multifocal abnormalities in subcortical white matter. Thalami, basal ganglia & brainstem also involved.
Anti-NMDAR	Hyperintensities on T2 FLAIR imaging in medial aspect of temporal lobes

HSV



JE





Step IV: Empirical Treatment

- Must be started if CSF cannot be done/report will take time and patient sick.
- Antibiotic in appropriate doses
- Acyclovir: 30mg/kg/day; can be stopped if
  - Diagnosis other than HSV is established
  - HSV PCR in the CSF is negative
  - MRI is normal
- Artesunate combination therapy (to be stopped if RDT and PS are negative)

Step V: Supportive care and treatment

a) Maintenance intravenous fluids : Isotonic fluids are preferred

b) Management of raised intracranial pressure:

- Head elevation,
- Minimal disturbance,
- Normothermia,
- Hyperventilation,
- Mannitol/ hypertonic saline

Supportive care and treatment

(c) Maintain euglycemia

(d) Treatment and prevention of seizures:

- If child is having seizures or has history of seizures
- Even in absence of seizures, if GCS <8 and features of raised ICT

(e) Other drugs : Corticosteroids, IVIG

(f) Other measures: Acid-base and electrolyte abnormalities should be corrected.

New drugs

- Pleconaril: enterovirus encephalitis and aseptic meningitis
- Minocycline : neuroprotective and antiviral

Step VI: Prevention/treatment of complications and rehabilitation

- Physiotherapy, posture change, Prevent bed sores and exposure keratitis.
- Complications: aspiration pneumonia, nosocomial infections, coagulation disturbances
- Nutrition: early feeding
- Psychological support to patient and family

Preventive strategies

(i) Surveillance for cases of AES;

(ii) Vector control;

(iii) Reduction in man-vector contact;

(iv) Vaccination

Case

- 14 yr girl with abnormal fluctuating behaviour & focal seizures over 6 weeks, abnormal posturing of right hand with involuntary perioral movements, refractory status epilepticus, mutism for 4 weeks
- No h/o fever, headache, myoclonic jerks, visual complaints, weight loss or any systemic complaints.
- At the time of admission, she was in encephalopathy with status epilepticus, and right upper limb dystonic posturing and perioral dyskinetic movements.
- During hospital stay: autonomic disturbances, respiratory distress

- Routine investigations were within normal limits. MRI brain and CSF studies were also normal.
- Her EEG showed generalised beta-delta range slowing with “delta brush” and focal epileptiform discharges as well.
- CSF anti-NMDA receptor antibody was positive.
- She received a course of intravenous methylprednisolone f/b IVIg
- She improved significantly. Presently she is on low dosage of steroids

EEG IN NMDAR ENCEPHALITIS

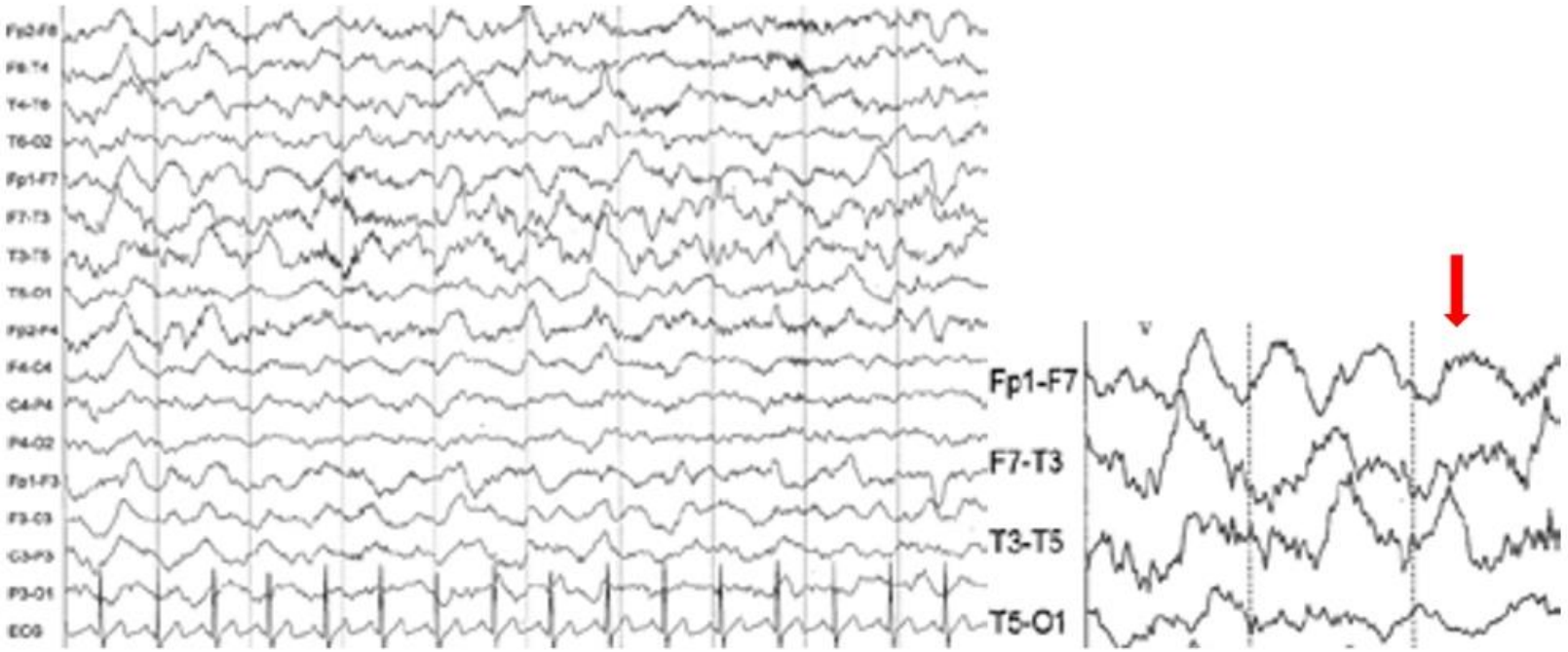


Fig. 2: EEG showing generalised theta-delta range slowing with serrated appearance of delta waves (due to overriding fast beta activity) in frontal area; representing extreme delta brush

Autoimmune encephalitis

- Group of neuropsychiatric disorders, presenting acutely or subacutely with alteration of consciousness, cognitive decline
- Associated with antibodies against neuronal cell surface proteins and synaptic receptors involved in synaptic transmission, plasticity or neuronal excitability
- More common in younger adults and children
- Severe and fatal but responds to immunotherapy
- Often associated with an underlying tumor

When to suspect autoimmune encephalitis?

- Polysymptomatic presentation- encephalopathy, seizures, movement disorders, psychiatric and autonomic disturbances
- Acute to subacute onset
- May follow a viral prodrome
- MRI and CSF normal or not suggestive of an infective process
- Deterioration after a period of improvement in a child with viral encephalitis

Clues to diagnosis of autoimmune encephalitis

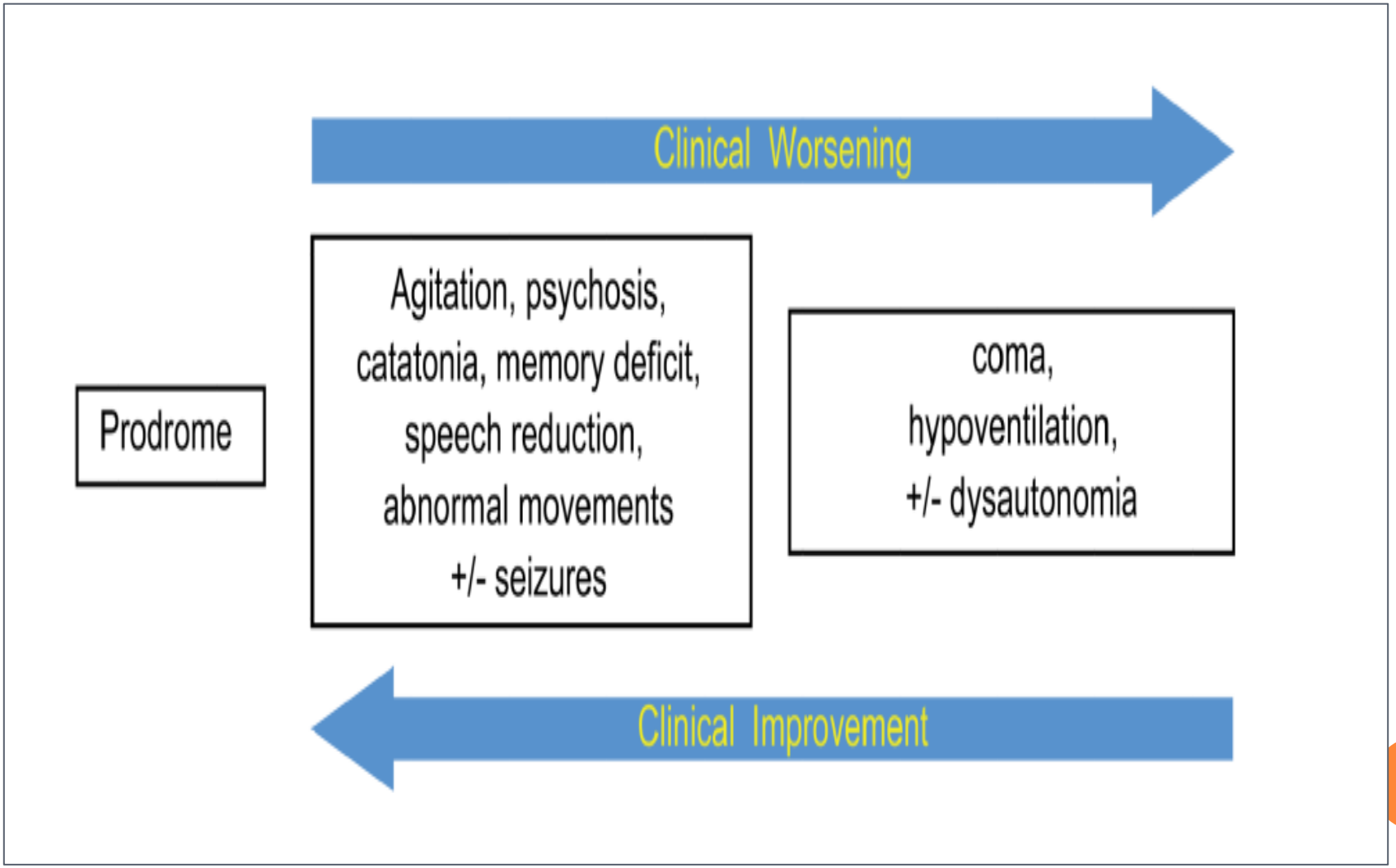
- Subacute onset of memory impairment (short term memory loss), encephalopathy or psychiatric symptoms
- At least one of the following
  - Focal neurological deficits
  - Unexplained seizures
  - CSF pleocytosis (WBC> 5 cells/mm3)
  - MRI features s/o encephalitis
- Exclusion of alternative causes

Khadilkar S et al. Autoimmune encephalitis: an update. Journal of the association of physicians of India. Vol 65. Feb 2017

Anti NMDA receptor Encephalitis

- Antibodies target NR1 subunit of NMDA receptor
- Disrupt function by cross linking and internalization of receptors
- 2nd MC cause of autoimmune encephalitis
- Predominates in females: 80%

Presentation….



Investigations

- MRI Brain: abnormal in 35% of patients
- Nonspecific findings like cortical and subcortical T2 FLAIR signal abnormalities; non specific white matter abnormalities seen
- EEG: extreme delta brush (beta-delta complexes)
- NMDAR antibodies in CSF and serum: higher sensitivity of CSF AB than serum and correlates better with outcomes

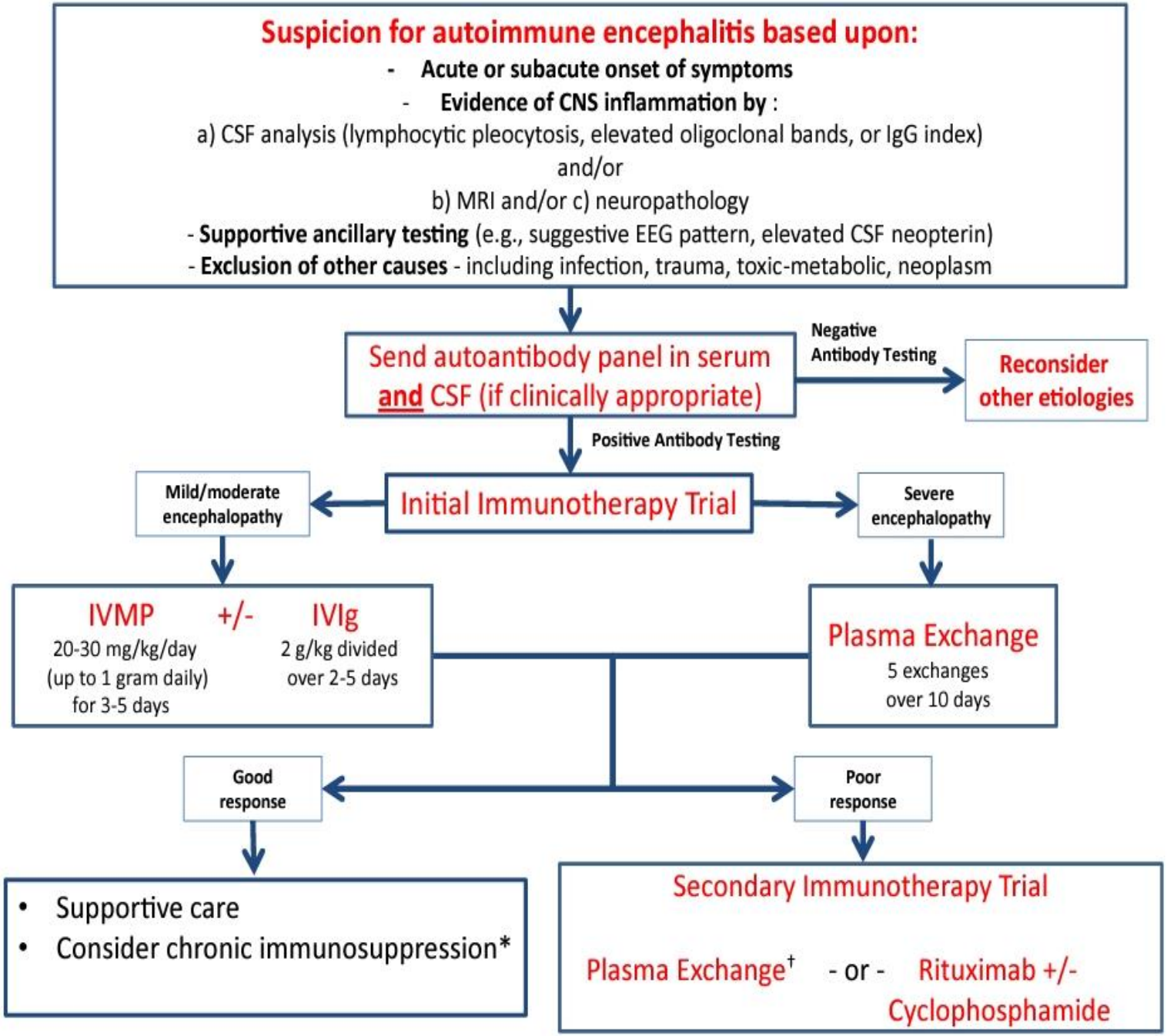
Diagnostic criteria: anti NMDAR encephalitis

1. Rapidly progressive following symptoms:
   - Abnormal behaviour or cognitive dysfunction
   - Decreased level of consciousness
   - Speech dysfunction
   - Seizures
   - Movement disorder, especially oral dyskinesias
   - Autonomic dysfunction or central hypoventilation
2. At least one of the following study results:
   - Abnormal EEG (slowing, epileptiform activity or extreme delta brush)
   - CSF pleocytosis or oligoclonal bands
3. Exclusion of other disorders
4. Accompanied by a systemic teratoma
5. IgG anti-GluN1 antibodies (Definite)

Khadilkar S et al. Autoimmune encephalitis: an update. Journal of the association of physicians of India. Vol 65. Feb 2017

Treatment

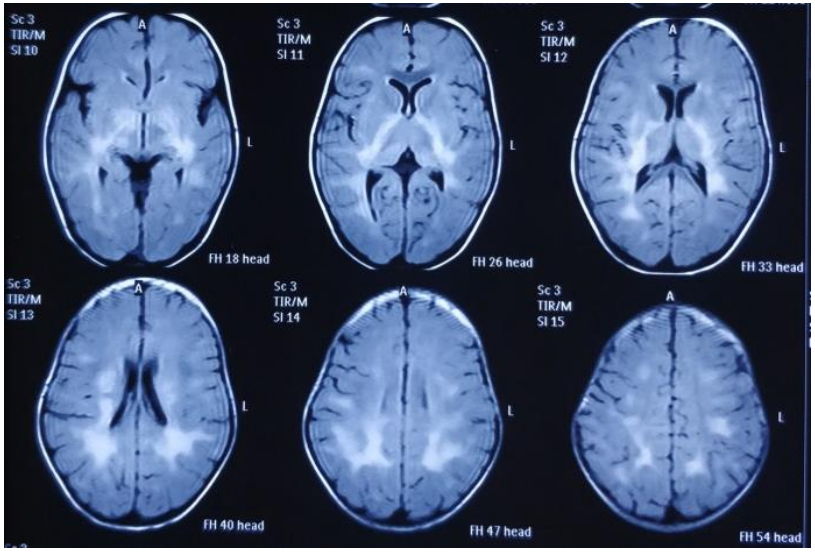
- First line immunotherapies: steroids, IVIG or plasmapheresis
- 2nd line agents: cyclophosphamide, rituximab
- Mortality rate of 7%
- 80% of patients have full or substantial recovery but can take as long as 2 years
- Relapse: 15% patients: milder but equal response to therapy

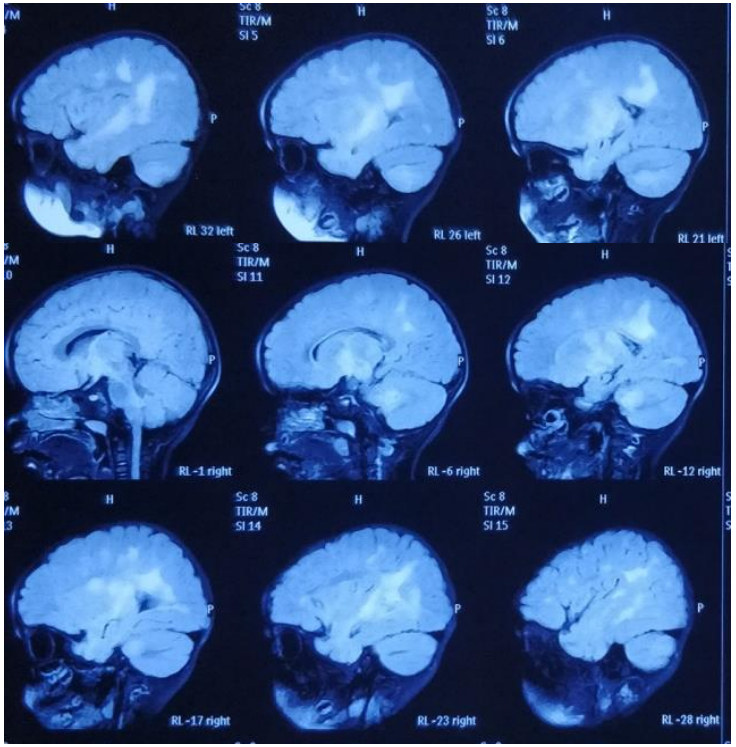

Suspicion for autoimmune encephalitis based upon:
- Acute or subacute onset of symptoms
- Evidence of CNS inflammation by :
a) CSF analysis (lymphocytic pleocytosis, elevated oligoclonal bands, or IgG index)
and/or
b) MRI and/or c) neuropathology
- Supportive ancillary testing (e.g., suggestive EEG pattern, elevated CSF neopterin)
- Exclusion of other causes - including infection, trauma, toxic-metabolic, neoplasm
Send autoantibody panel in serum and CSF (if clinically appropriate)
Negative Antibody Testing
Reconsider other etiologies
Positive Antibody Testing
Mild/moderate encephalopathy
Initial Immunotherapy Trial
Severe encephalopathy
IVMP +/- IVIg
20-30 mg/kg/day (up to 1 gram daily) for 3-5 days
2 g/kg divided over 2-5 days
Plasma Exchange
5 exchanges over 10 days
Good response
Poor response
• Supportive care
• Consider chronic immunosuppression*
Secondary Immunotherapy Trial
Plasma Exchange† - or - Rituximab +/- Cyclophosphamide

Case

- A 4 year old girl came to OPD with C/O:
  - Sudden onset weakness of left side of body- 5 days
  - Deviation of left side of mouth
  - Irritability
- No c/o fever, seizure, bladder/bowel incontinence, no deviation of eyes or change in voice or nasal regurtitation or blurred vision
- No h/o recent vaccination, or any viral illness
- Developmentally normal child premorbidly
- On examination: child was irritable
- Right upper motor neuron type facial nerve palsy present

MRI BRAIN





Large, multifocal and confluent or large oedematous mass like tumefactive T2 lesions
Deep gray matter structures (thalami, basal ganglia) are often involved

ADEM

- Inflammatory, demyelinating event with multifocal neurological deficits accompanied by encephalopathy
- Pathogenesis: molecular mimicry
- Influenza, EBV, CMV, varicella, enterovirus, measles, mumps, rubella, HSV and mycoplasma pneumoniae
- Post vaccination: rabies, smallpox, measles, mumps, rubella, JE B vaccine, DPT

ADEM

- Non specific neurological features
- CSF: lymphocytic pleocytosis, protein-elevated
- EEG: generalized slowing (polyregional demyelination- focal slowing or epileptoform discharges)
- Treatment
  - High dose corticosteroids f/b oral steroids
  - IVIG/ plasmapheresis
  - Rituximab/ cyclophosphamide: severe cases

Key messages

- Most important part of managing a patient of AES is to stabilize the patient
- Managing the ongoing seizures and features of raised ICT
- Empirical treatment has to be started as soon as possible without delay and after appropriate investigations, antivirals/ antimalarials can be stopped.

READING MATERAIL

- GHAI'S TEXTBOOK OF PEDIATRICS
- NELSON'S TEXTBOOK OF PEDIATRICS

JAPANESE B ENCEPHALITIS

HISTORY

- Epidemics of encephalitis - Japan from the late 1800s.
- First isolated in Japan during an epidemic in 1935.
- In India first recognized in 1955 in Vellore.
- JE is a positive sense single stranded RNA virus.
- Family of Flaviviridae.

EPIDEMIOLOGY

- Annual incidence in endemic areas 1-10/10,000 population.
- Children <15 yr of age are principally affected.
- Highly endemic areas - A P, T N, Karnataka & UP.
- Peak starts after rains- July to December.

TRANSMISSION

- Transmitted as zoonotic cycle

  - Mosquito
  - Culex tritaeniorhynchus
  - Culex vishnui

  Vertebrates like-
  Pigs & wading birds
  Pigeon, Sparrow,
  Duck, Horses, Swine,
  Cattle & Buffalo

- Humans are dead end host.

- Pigs serve as amplifying host.

PATHOLOGY

- Areas of brain most commonly thalamus, substantia nigra, anterior horns of spinal cord, Cerebral cortex and cerebellum

- Other organs affected are: Lymph nodes, spleen, myocardium, lungs and kidney

- After transmission virus multiplies locally and in regional nodes- transient viremia- invasion of CNS- in the neurons virus multiplies in the neuronal secretary system

PATHOLOGY CONT.

- Affect endoplasmic reticulam & Golgi apparatus and destroy them.
- After primary infection IgM response in serum and CSF usually within 7 days.
- Immunization with inactivated JE vaccine induces T cell activation in vivo.

CLINICAL FEATURES

- Incubation period 1 to 14 days.
- Onset is abrupt, acute, sub-acute or gradual.
- Typically progress through 4 stages
  Prodromal stage: 2 to 3 days
  Acute stage (3-4 days)
  Sub acute stage (-10 days)
  Convalescence (4- 7 wk)

PRODROMAL STAGE

Abrupt onset of high grade fever

Head ache

Malaise

Abdominal pain

Nausea & vomiting

Sensory changes and psychotic episodes.

ACUTE STAGE

- Neurological symptoms 3 to 5 days
- Altered sensorium, Convulsions
- Neck stiffness, muscular rigidity
- Mask like facies, ICT
- Characteristic are rapidly changing central nervous system signs .
- Gastric hemorrhage, pulmonary edema

CONVALESCENCE STAGE

- Stage of recovery
- Slowly regain neurological function over several weeks
- Speech defects
- Paresis
- Intellectual deficit

DIAGNOSIS

- CSF: pleocytosis (100-1000 leukocytes/mm3)

  Increased protein

  Normal glucose

- CT: involvement of thalamus, basal ganglia,

  mid brain, pons & medulla

- EEG: diffuse theta & delta waves

ETIOLOGICAL DIAGNOSIS

- Four fold rise or greater in serum antibody.
- Isolation of virus/ demonstration of viral antigen or genomic sequences .
- IgM capture Elisa

STANDARD CASE DEFINITION

- Suspect case of JE- clinical description
- Probable JE- presumptive lab results
- Confirmed JE- confirmatory lab results
- Antigen or genome in tissues or blood by immune chemistry or immune fluorescence or by PCR
- JE virus specific IgM in CSF
- 4 fold or greater rise in JE virus specific antibody in paired sera

PRESUMPTIVE LAB DIAGNOSIS

- Detection of acute phase antiviral antibody response by any one of the following
  - Increased and stable serum antibody titres of JEV by ELISA.
  - Hemagglutination or virus neutralization assay

    IgM antibody to the virus in serum.

DIFFERENTIAL DIAGNOSIS

- West Nile virus
- Entero virus
- Herpes virus
- CNS tumors
- SLE
- Enteric encephalopathy

TREATMENT

- No specific treatment.
- Symptomatic & supportive aimed at prevention of

  Pulmonary aspiration, hypoxia

  Hypoglycemia, hyper pyrexia

  Uncontrolled seizures, raised ICT

  Pulmonary edema, SIADH

  Secondary infection, brainstem involvement

TREATMENT CONT..

- Airway, breathing & circulation
- Seizures: Diazepam, Valproate
- Fluid, electrolyte & blood sugar maintained
- Raised ICT: Hyperosmolar therapy
- Coma - prevent aspiration, bedsores, nosocomial infection, malnutrition & contractures
- Extra pyramidal symptoms: Haloperidol, Diazepam, chloral hydrate

SPECIFIC THERAPY

- Monoclonal antibodies

- Recombinant Interferon alpha

PROGNOSIS

- Patient fatality rates are 24-42%.
- Frequency of sequelae is 5-70% and is directly related to the age of the patient and severity of the disease.
- Most common sequelae are mental retardation, severe emotional instability, personality changes, motor abnormalities and speech disturbances.

PROGNOSIS

- Poor prognostic signs are:
  Younger age
  Hyponatremia
  Shock
  Low GCS
  Presence of immune complexes in CSF
  Increased levels of tumor necrosis factor

- Good prognostic sign: high levels of neutralizing antibodies (IgG) in CSF

PREVENTION

- Control of mosquito: insecticide, fogging, larvicidal measures & pyrethrum.
- Prevention of bites: Avoid out door activities, clothing, mosquito repellants, bed nets or house screening.
- Control/ protection of reservoirs, piggeries, vaccination in pigs- decrease viral amplification.
- Vaccination in high risk areas, susceptible population

VACCINATION

- Travelers to endemic countries who plan to be in rural areas of the endemic region during the expected period of seasonal transmission.

- Travelers in rural areas experiencing endemic transmission should receive JE vaccine.

- In humans, prior dengue virus infection provides partial protection from clinical JE.

VACCINATION

- Inactivated mouse brain vaccine- Nakayama strain- dose: 0.5- l ml SC – 1 to 3 years- 3 doses- 0-7-10 days, booster every 3 years- till 10-15 years

- Inactivated primary hamster kidney cells- China- SC 0.5ml- 1to2 years- booster 6 yrs -cheap

- Live attenuated primary hamster kidney cells- cheap- single dose- not approved by WHO

VACCINATION CONT.

- Vaccination of travelers- 0-7-30

- The final dose should be completed at least 1 wk prior to the patient's expected arrival in a JE endemic area.

Newer vaccines:-

- Recombinant JE vaccine
- DNA multivalent vaccine
- Chimeric vaccine

READINGS :

Nelson’s Textbook of Pediatrics 20th Edition

Ghai’s Textbook of Pediatrics

QUESTIONS :

What is the vaccination schedule for Japanese encephalitis?

What are the MRI findings in Japanese encephalitis and HSV encephalitis?

Define Encephalitis and Encephalopathy?

Enumerate various causes of Acute Encephalopathy Syndrome(AES)?

How we should manage AES?