Japanese Encephalitis clinical perspectives

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Introduction

- **Mosquito borne arboviral diseases have become a significant public health concern worldwide and the most populated Southeast Asian region is particularly vulnerable.**

- **Diseases such as dengue (DEN), Japanese encephalitis (JE) and chikungunya fever (CHIK) are on the rise and have spread unprecedentedly, causing considerable burden of disease in Southeast Asia including Myanmar.**

Japanese encephalitis

- Estimated 35,000 to 50,000 cases worldwide
  - fatality rate - approximately 25%
  - Transmitted by *Culex* mosquitoes (*C. tritaeniorhynchus)*
- Pigs are important amplifier hosts

JE in Myanmar

- The first confirmed outbreak of the disease in human was in Tachileik in 1974
- Another outbreak occurred in Lashio during the following year 1975.
- The outbreak occurred in horses at the animal breeding center in Bahtoo in 1977.
- The virus was first isolated from the diseased horse's brain (confirmed by the WHO reference center in Poona, India)

JE genome structure

- JE, is a member of the genus *Flavivirus* in the family *Flaviviridae.* Similar to other flaviviruses like dengue comprising 3 structural and 7 nonstructural proteins.

- JE is a vaccine preventable disease.

  Currently used (Genotype III) vaccines. Conducting surveillance (genotypic studies) can detect changing strains and new emergence.

- In Myanmar, there are a lot of sero-prevalence studies regarding JE virus, but very little genotypic studies.

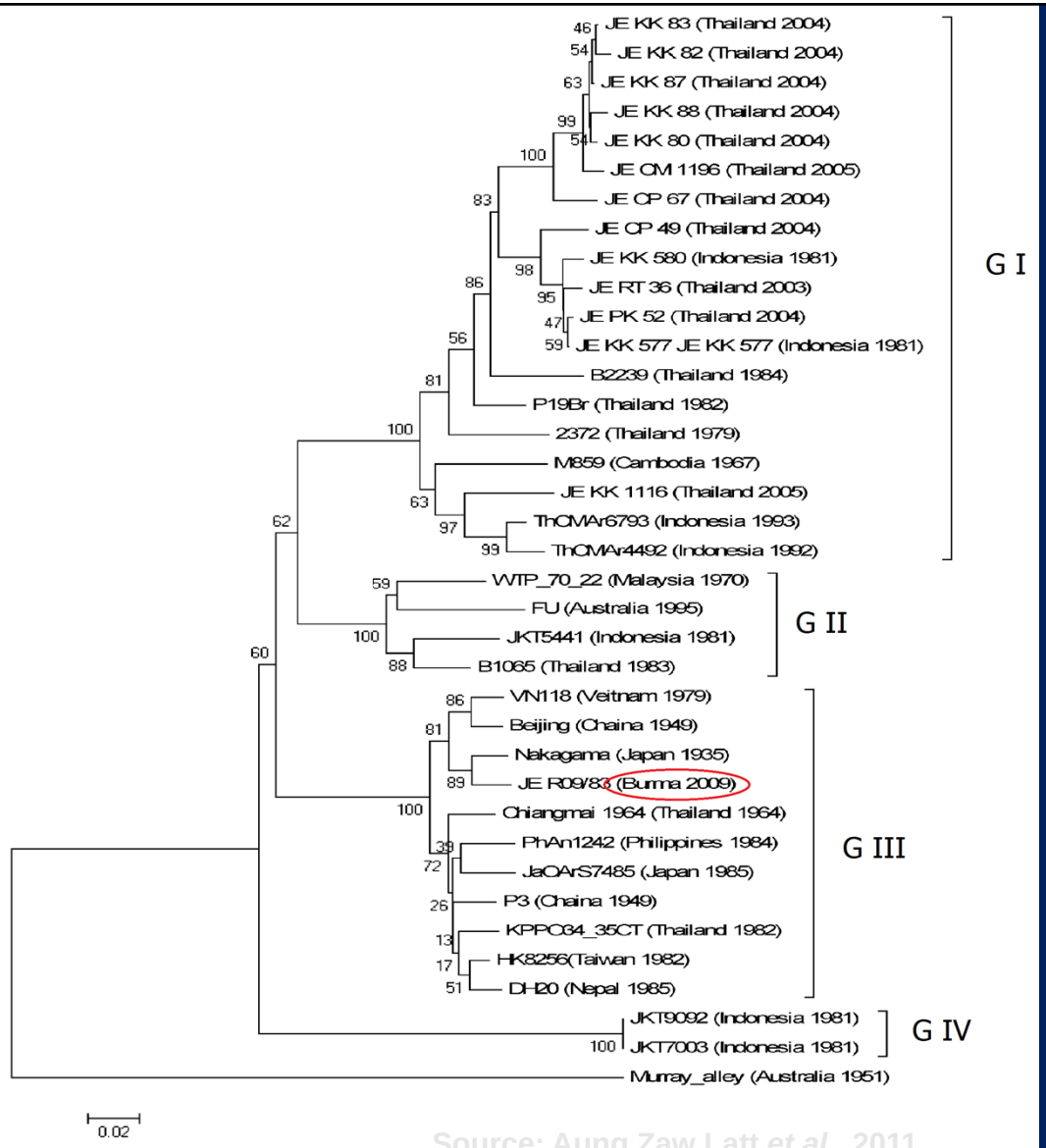
- **Phylogenetic studies indicate that JEV can be classified into five genotypes based on nucleotide sequences of the E protein gene.**

- **The first JE virus sequenced in Myanmar was on a virus isolated from pigs, from a Dike Oo pig farm (70 miles from Yangon) in 2009.**

- **The 1,414 nucleotides generated partial sequences of the JEV E gene that were compiled by using Sequence-Alignment Editor version 5.0.9 ; pairwise genetic distances were calculated with MEGA version 4.0.**

- **Phylogenetic analysis was done and the JEV circulating was genotype III.**

Phylogenetic analysis of JE viruses from Dike Oo township. Using the neighbor-joining (p-distance) method. The length of the tree branches indicates the percentage of divergence the percentage of successful bootstrap replicates is specified at the nodes (1,000 replicates). Murray valley virus prototype sequence was included to root the tree.

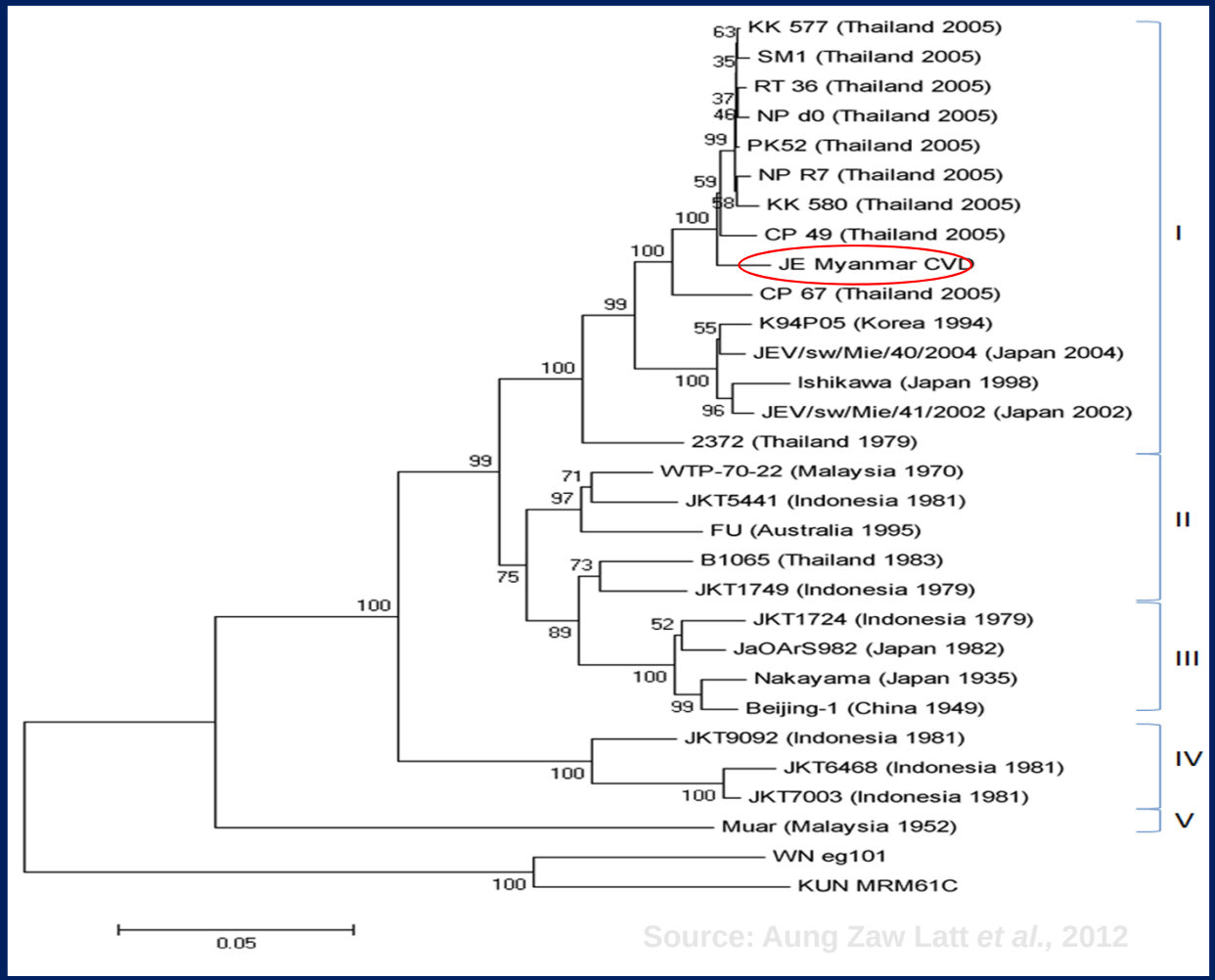


Source: Aung Zaw Latt *et al.*, 2011

- **In another molecular epidemiology study, JE virus was isolated from a pig farm in Thaketa township in 2010.**

- **Phylogenetic analysis was done using 27 previously published JEV global sequences including those from Thailand (11), Japan(5), Indonesia (6),Malaysia (2) , Korea(1) , Australia (1) and China (1).**

- **A phylogenetic tree was generated revealing that the new Myanmar JE virus isolate from Thaketa township was Genotype I closely related to virus strains from Southern Thailand from the year 2005.**



Phylogenetic analysis of E gene from JEV isolated from Thaketa, Yangon, 2010

- Recent data from other countries around the world indicate that genotype I (GI) is gradually replacing genotype III (GIII) as the dominant genotype.

- The differences between the two genotypes was analysed by investigating amino acid mutations, positive selection, and host range.

- The results suggest that GI has displaced GIII by achieving a replication cycle that is more efficient but more restricted in host range. In particular, the narrow range suggests that the GI strain has been optimized for transmission to and from *Culex tritaeniorhynchus* and pigs.

JE vaccines

- There are two types of JE vaccines currently available internationally and several in late-stage development.
- Some countries have conducted routine immunization with an **inactivated, mouse brain-derived JE vaccine** for many years.
- The **live, attenuated** SA 14-14-2 vaccine has been used in China for almost 20 years and more recently in several other countries.

CHILDREN WITH JAPANESE ENCEPHALITIS IN MYANMAR – CLINICAL EPRSPECTIVE

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Yangon Children Hospital

Viral encephalitis in Myanmar - 1

- A study from 1988 to 1989 – Yangon children hospital
- Total – 41 children
- Viral etiological agents of encephalitis were
  - Japanese B encephalitis (19.5%)
  - Enteroviruses (17.1%)
  - Herpes simplex virus (4.9%)
  - Mumps (2.4%)
  - Remaining 56.1% - unknown etiology

Khin Nu Thar, 1990

Khin Nu Tha, 1990

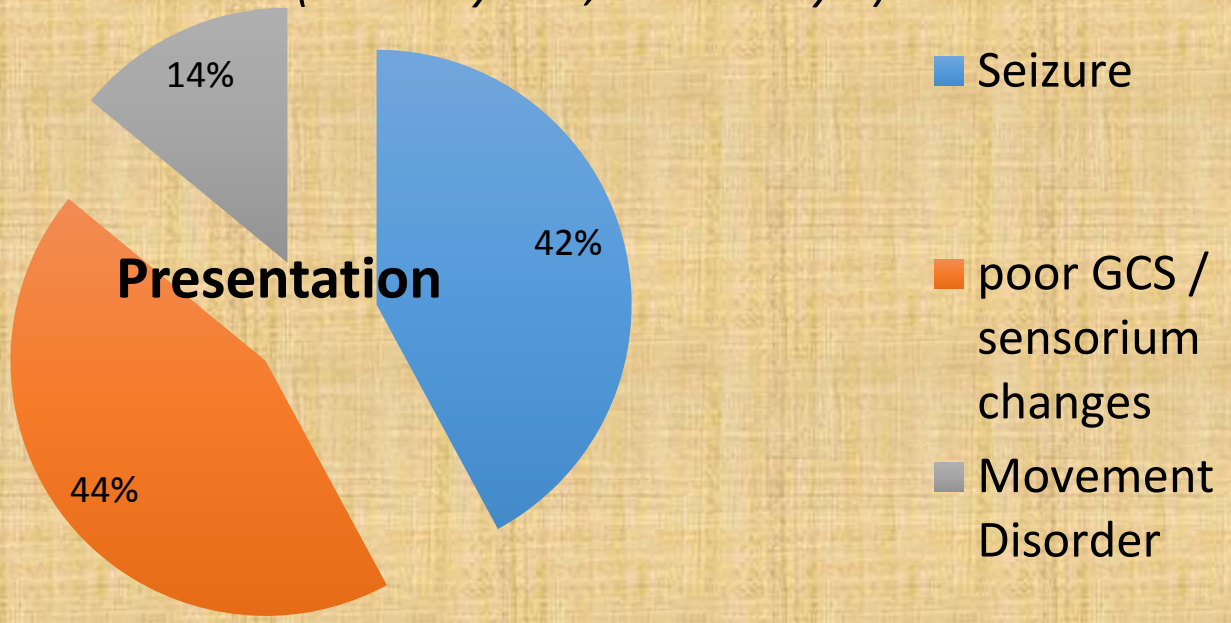
Viral encephalitis in Myanmar - 2

- Total - 57 children – Yangon children hospital
- Japanese B encephalitis -12.5%,
- Dengue encephalitis - 28.6%

Thuzar Win Han, 2010

Study on children with possible encephalitis Yangon children hospital, 2013

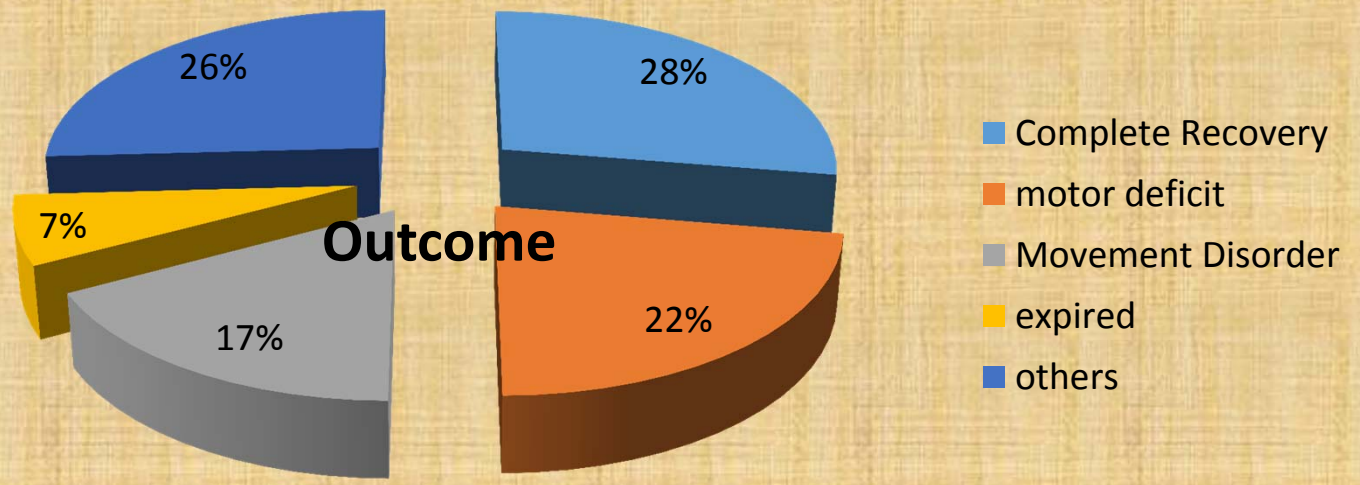
Total 58 children (0.1- 12 years, mean 4.6yrs)



Majority – late referral, self-treated with oral antibiotics

Sanda ko, kyaw linn, 2013

Study on children with possible encephalitis Yangon children hospital, 2013



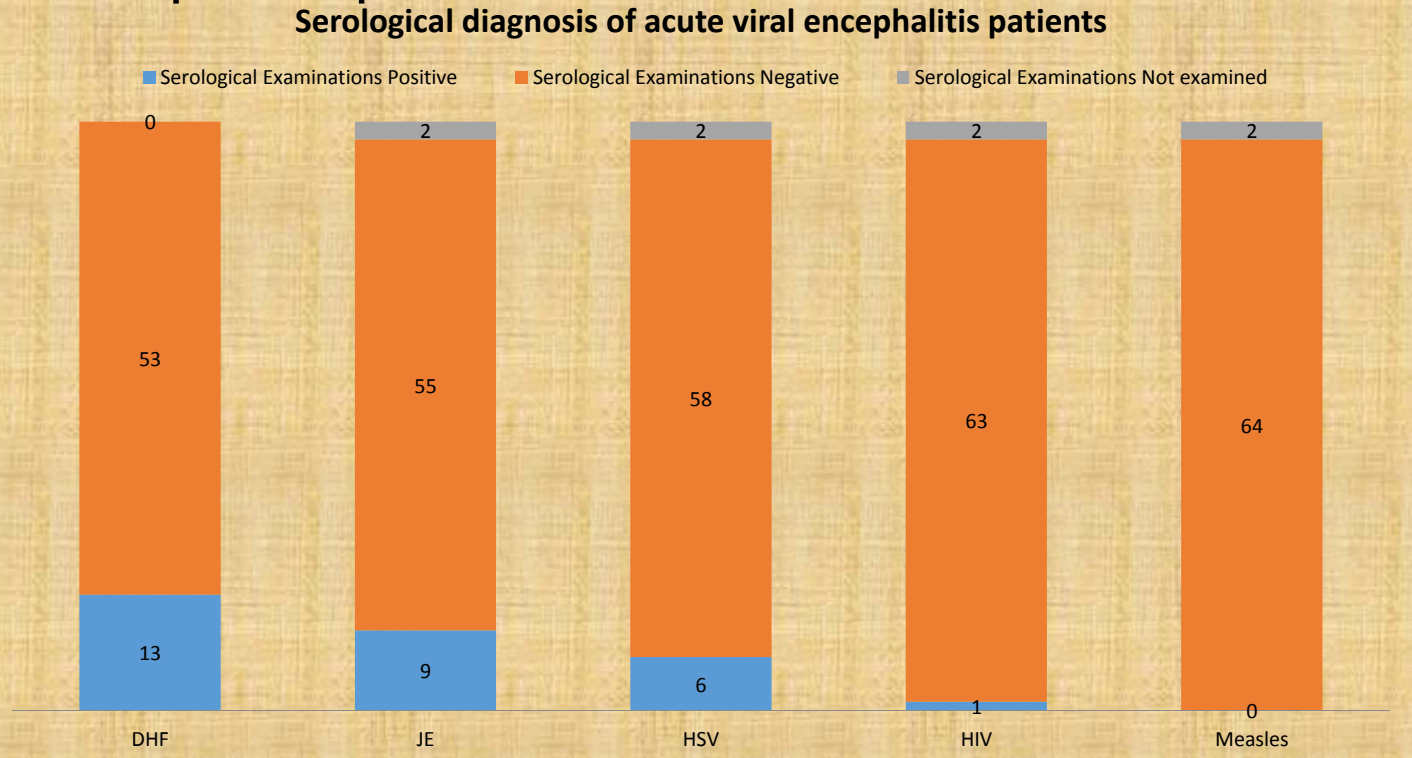
Sanda ko, kyaw linn, 2013

Study on children with encephalitis in Yankin, Thingungyun and North-Okkalapa hospitals – 2013

Age	No.	Percent
1 month – 1 year	15	22.7
1-5 years	26	39.4
5-12 years	25	37.9
Total	66	100

Wai Wai Nwe, 2013

Study on children with encephalitis in Yankin, Thingungyun and North-Okkalapa hospitals - 2013



Wai Wai Nwe, 2013

2014
Total admission to Yangon children hospital - 18690

	Admission	Death
Meningitis	181	11
Encephalitis	138	15
Total CNS infections	319	26

2014 – Brain infections

Meningitis

	Total	Death
Under 5	140	10
Above 5	41	1

Encephalitis

	Total	Death
Under 5	81	11
Above 5	57	4

2014 – Brain infections

Meningitis

	Total	Death
Under 5	**140**	**10**
Above 5	41	1

Encephalitis

	Total	Death
Under 5	**81**	**11**
Above 5	57	4

Leading causes of under 5 deaths in Myanmar

1. Respiratory tract infections
2. Diarrhoea
3. Brain infections
4. Malaria
5. Beri beri
6. Septicaemia

Myanmar health statistics-2013

Consciousness

- dependent on the function of two separate anatomical and physiological syetems:

1. The ascending reticular activationg sys(ARAS) projecting from brainstem to thalamus.{determines arousal}(the level of consciousness)
2. The cerebral cortex: determines the content of consciousness

Impaired functioning of either anatomical system may cause coma

Disturbed consciousness: def

- Coma- a state of unrousable unresponsiveness.
- Level of consciousness represents a continuum between being alert and deeply conmatose.
- It may be qualified using the GCS
- Coma→ GCS < 8

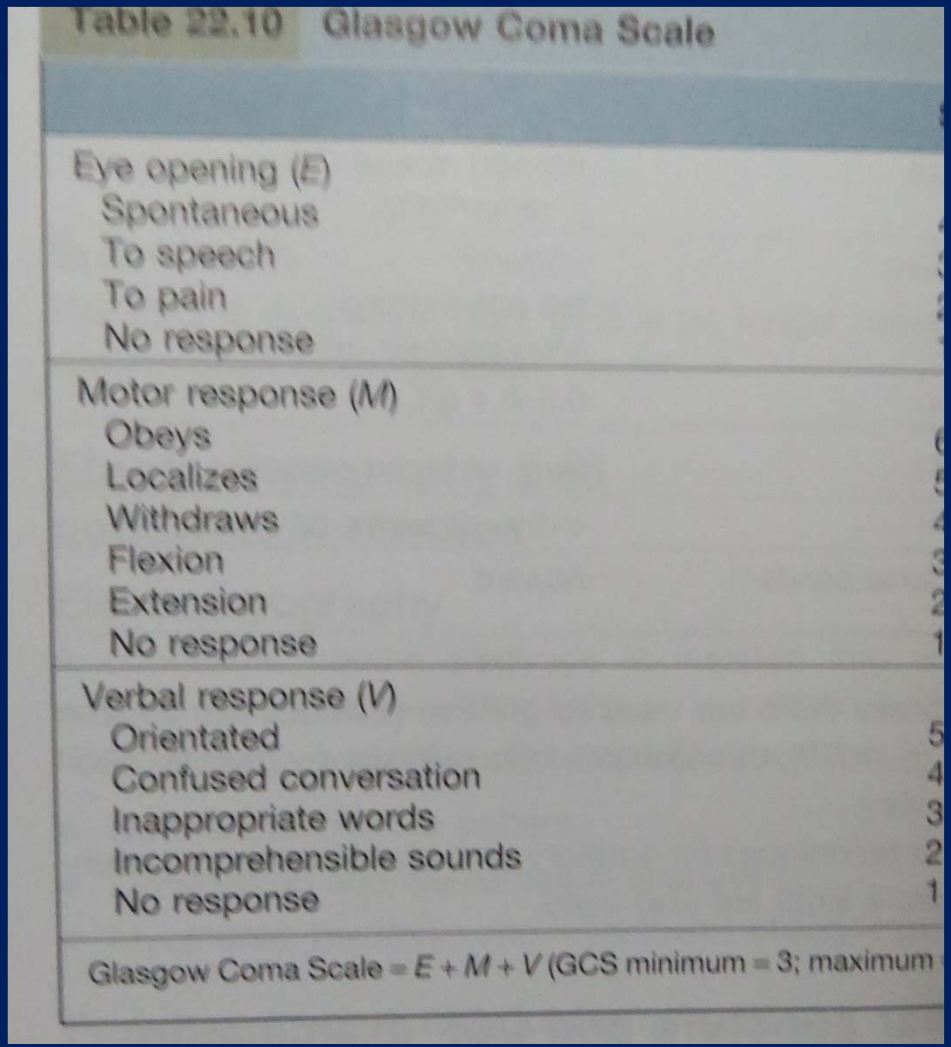


Table 22.10 Glasgow Coma Scale

Eye opening (*E*)	
Spontaneous	4
To speech	3
To pain	2
No response	1
Motor response (*M*)	
Obeys	6
Localizes	5
Withdraws	4
Flexion	3
Extension	2
No response	1
Verbal response (*V*)	
Orientated	5
Confused conversation	4
Inappropriate words	3
Incomprehensible sounds	2
No response	1

Glasgow Coma Scale = *E* + *M* + *V* (GCS minimum = 3; maximum

- Glasgow Coma Scale
- EMV=minimum 3
- Maximum=15

delirium

- The term used to describe a confusional state in which reduced attention is a cardinal feature, usually with altered behavior, coginition , orientation and a fluctuating level of consciousness from agitation to hypoarousal

Stupor and obtundation

- No longer use

Principle causes

- Diffuse brain dysfunction
- Direct effect within brainstem
- Pressure effect on brainstem

Diffuse brain dysfunction

- Drug overdose
- Encephalitis, meningitis, cerebral malaria
- SAH
- CO poisoning
- Trauma to brain
- Hypo,hyperglycemia
- Organ failure- severe uraemia,hepatic encephalopathy,respira

Continue:

- Hypercalcaemia, hypoCa
- Hypoadrenalism, hypopit and hypothyroidism
- Hyponatraemia, hypernatraemia
- Metabolic acidosis
- Hypothermia, hyperpyrexia
- Seizures-post epileptic state, non-convulsive state

Continue;

- Metabolic rarities eg porphyria
- Extensive cortical damage
- Hypoxic ischaemic brain injury eg cardiac arrest

Direct effect within brain stem

- Brainstem haemorrhage, infarction or demyelination
- Brainstem neoplasm eg glioma
- Wernicke-korsakoff syndrome

Pressure effect on brainstem

- Tumor, massive hemisphere infarction with edema
- Haematoma,
- Abscess
- Cerebellar mass

mechanism

- Altered consciousness is produced by four mechanisms affecting the ARAS in the brainstem or thalamus, and / or widespread impairment of cortical function

- Brain stem lesion- a discrete brainstem or thalamic lesion, eg stroke may damage the ARAS
- Brainstem compression: a supratentorial mass lesion within the brain compresses the brainstem, inhibiting the ARAS, ge coning from a brain tumour or haemorrhage. Mass lesion within the post fossa→ prone to cause and hydrocephalous

Diffuse brain dysfunction

- Diffuse brain dysfunction: generalized severe metabolic or toxic disorders(eg alcohol, sedatives, uraemia, hypercapnia,depress cortical and ARAS function)

Massive cortical damage

- Unlike brainstem lesion, extensive damage of the cerebral cortex and cortical connections is required to cause coma, eg meningitis or hypoxic-ischaemic damage after cardiac arrest
- A single focal hemisphere or cerebellar lesion does not reduce coma unless it compresses the brain stem.
- Cerebral edema frequently surrounds masses, increasing their pressure effects.

Commonest causes of coma are:

- Metabolic disorder 35%
- Drug and toxin- 25%
- Mass lesion 20%
- Others- including trauma, stroke and CNS infectiona

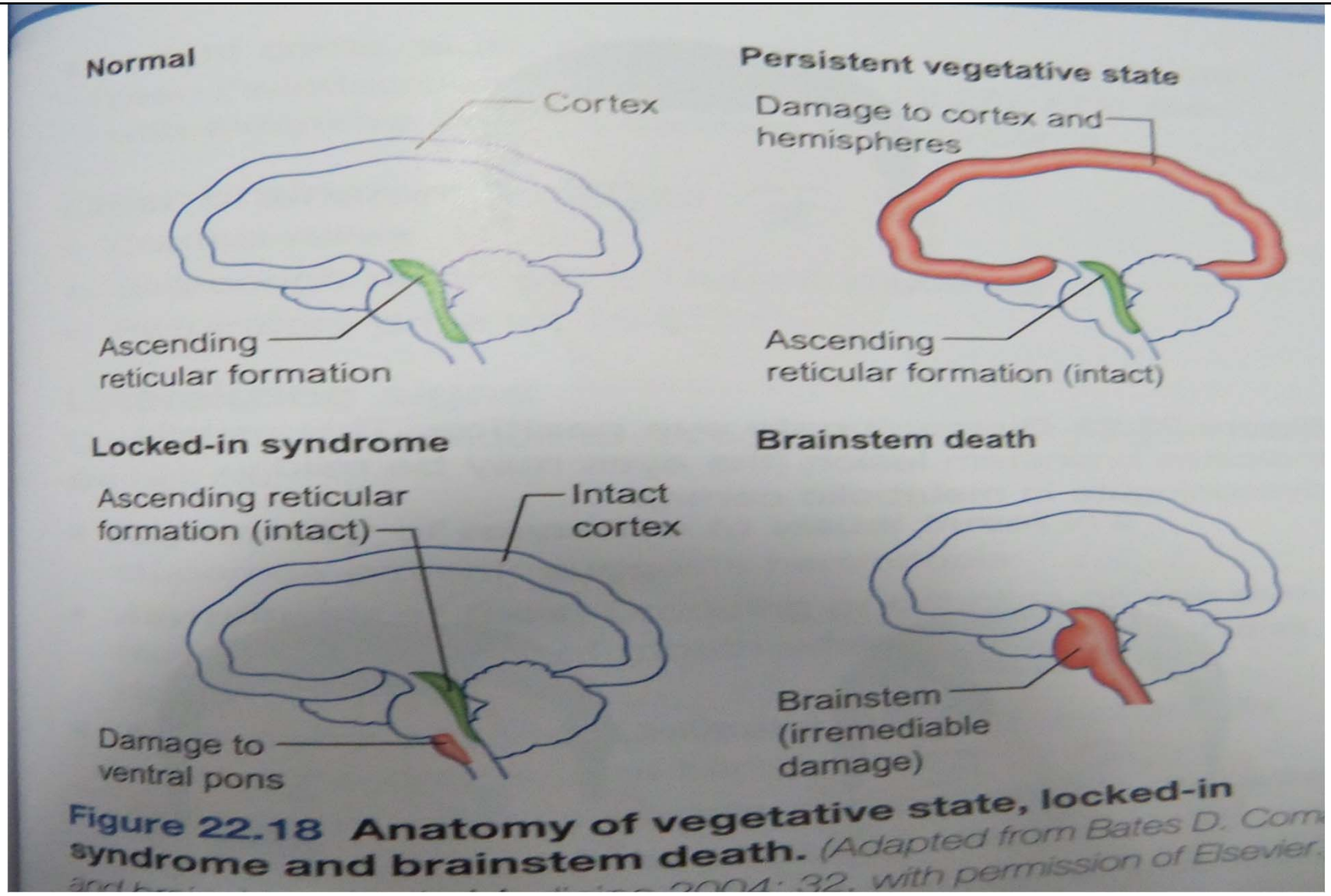


Figure 22.18 Anatomy of vegetative state, locked-in syndrome and brainstem death. *(Adapted from Bates D. Com*
and br... 2004; 32, with permission of Elsevier

Immediate assessment and management

- Check the airway, breathing and circulation
- Stix for blood glucose: if hypo- give glucose (25ml 50%)
- Treat seizures with buccal midazolam and if not terminated, intravenous phenytoin
- If there is fever and meninism: give IV antibiotics
  check ICT malaria or blood film

What is Nervous System infection?

Nervous system infection

- Meningitis
- Encephalitis
- HIV
- Neurosyphilis
- Neurocysticercosis
- Herpes zoster(shingles)
- Abscess(brain and spinal)
- Other infection- rabies, tetanus, botulism, lyme disease, leprosy
- Other inflammatory condition

Other inflammatory conditions

- Subacute sclerosing panencephalitis (SSPE)
  - Persistence of measles antigen in the CNS
- Progressive rubella encephalitis-rare
- Mollaret's meningitis- recurrent self limiting episodes of aseptic meningitis (no bacteria cause found)
- Whipple's disease
- Neurosarcoidosis
- Behcet's syndrome- orogenital ulcer, ocular disease, neuro: brain stem and cord lesion,aspetic meningitis encephalitis and cerebral venous thrombosis

encephalitis

- Acute inflammation of brain parenchyma, usually viral.
- In viral encephalitis fever (90%) and meningism are usual, but in contrast to meningitis the clinical picture is dominated by brain parenchyma inflammation.
- Personality and behavioural change is a common early manifestation which progresses to a reduced level of consciousness and even coma.
- Seizures (focal and generalized) are very common and focal neurological deficits, eg speech disturbance, often occur (especially in herpes simplex encephalitis).

Investigation

- MRI- imaging shows areas of inflammation and swelling generally in the temporal lobes in HSV encephalitis,Raised ICP and midline shift
- EEG –periodic sharp and slow wave complexes
- CSF- elevated lymphocytes count (95%)
- Viral detection by CSF PCR is highly sensitive for several viruses such as HSV and VZV
- Brain biopsy rarely required since the advent of MRI and PCR

Treatment

- Suspected HSV ad VZV encephalitis is treated immediately with IV acyclovir (10mg/Kg 3 times a day for 14-21 days), even before investigation results are available.
- Early treatment significantly reduces both mortality and long-term neurological damage in survivors.
- Seizures are treated with anticonvulsants
- Occasionally decompressive craniectomy is required to prevent coning but coma confers a poor prognosis.
- Long term complication are common including memory impairment, personality change and epilepsy.

Our approach to CNS infection - 1

- Always give treatment for bacterial meningitis
  - Might withdrawal antibiotics if CSF normal
- IV cefotaxime/ceftriaxone – first line
- Change to Vancomycin (2nd line) if
  - Not responding to 1st line antibiotics after 48 hours
- Microbiological diagnosis – mostly not possible
- Duration of antibiotics – 2 weeks

Our approach to CNS infection - 2

- TB meningitis considered when
  - Long duration of fever
  - Previous constitutional symptoms for TB
  - TB contact
  - Lack of BCG immunization
  - CSF high protein, lymphocytosis
  - Not responding to treatment with bacterial meningitis

Our approach to CNS infection - 3

- viral encephalitis considered when
  - Short duration/ acute onset
  - Multiple seizures/status
  - Movement disorders
  - Mood/sensorium changes
  - CSF – normal/mild lymphocytosis
  - EEG – generalized slowing
- IV Acyclovir - not always used
- Routine testing for Herpes simplex – not possible

Our approach to CNS infection - 4

- Autoimmune encephalitis considered when
  - Phenotypically similar to autoimmune encephalitis syndromes
  - Example
    - NMDA encephalitis if behavioral/psyschiatric symptoms
    - ADEM if both cerebral and spinal s/s present
  - Especially if clinical, white cell count, CRP, CSF features are not like infection
- Autoimmune panel not available in Myanmar

Autoimmune encephalitis

- Autoantibodies directed against neuronal epitopes cause a subacute encephalitic illness – limbic encephalitis or panencephalitis.
- Limbic encephalitis presents over weeks or months with memory impairement, confusion, psychiatric disturbance, and seizures – usually TLE reflecting involvement of the hippocampus and mesial temporal lobes.
  - Paraneoplastic limbic encephalitis(PLE)-small cell lung cancer
  - Voltage gated potassium channel (VGCK) limbic encephalitis- VGCK antibodies produce a variety of disorders ,>50 years
  - antiNMDA receptor antibody panencephalitis-limbic encephalitis

Treatment of autoimmune encephalitis

- Responds to immunotherapy-
  - IV immunoglobulin or plasma exchange initially followed by steroids,rituximab or cyclophosphamide
  - PLE responds less well

Management ?

Management

- Step I: Rapid assessment and stabilization
- Step II: Clinical evaluation: History and Examination
- Step III: Investigation/Samples to be collected
  - CP, CRP
  - Blood malaria parasite, ICT malaria
  - Chest X ray
  - CSF – only routine exam & culture
  - Imaging ?

Management

- Step IV: Empirical
  - IV cefotaxime/ ceftriaxone
  - ?IV aciclovir
- Step V: Supportive care and treatment

- Step VI: Prevention/treatment of complications and rehabilitation

Problems in our management - 1

- Paucity of data about the epidemiology and etiology of viral encephalitis

- Lack of easily available, low-cost microbiological testing for agents of viral encephalitis

Problems in our management - 2

- Lack of specific treatments especially aciclovir
- High incidence of mimickers - pyogenic meningitis, cerebral malaria, tubercular meningitis, acute desseminated encephaloyelitis etc.

Problems in our management - 3

- Lack of facilities for intensive care in the periphery
- Lack of facilities for neuroimaging in the periphery.
- Inappropriate response during epidemics - what samples to take, how to store, whom to inform, etc.

Problems in our management - 4

- Patient delay in seeking health care
- Delay/not performing lumbar punctures
- Inadequate supporting teams