CNS module / 3rd year medicine

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Neuroscience 2 / Lecture 1

1. *Clostridium botulinum*
2. *Clostridium tetani*
3. Prion diseases

Clostridium botulinum

- Characteristics:

- Gram positive anaerobic rods (appear as gram negative in old cultures)
- Motile by flagella

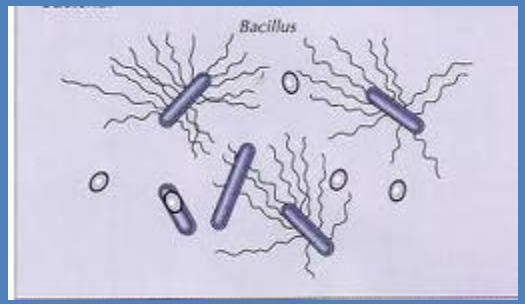
- Seven main types A-G: A, B and E are the commonest

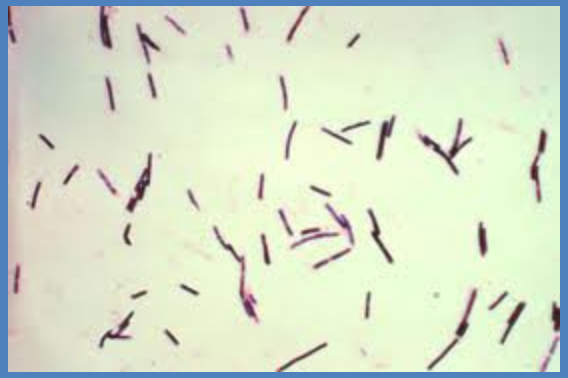
- Each secretes antigenically distinct but functionally similar toxin (very potent)
- Grows better at 35°C but some strains grow at 1-5 °C

Clostridium botulinum

- It forms spores:

- Heat resistant
- Widely distributed in the environment; SOIL, water, vegetable, fruit meat, honey..
- Oval and subterminal

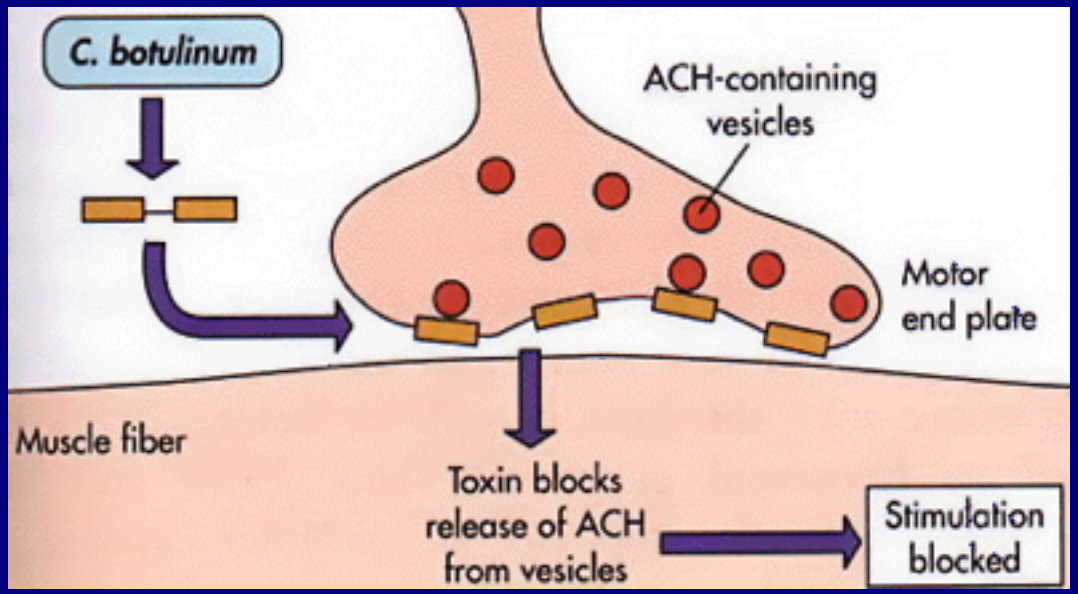




Clostridium botulinum

- Pathogenesis:

Neurotoxin production > stomach absorption > circulation > neuromuscular junction (NMJ) > inhibition of acetylcholine release at the NMJ > flaccid descending motor paralysis



Clostridium botulinum

- The toxin (heat labile):

1. Preformed in food that is badly preserved and processed (hygiene and heat) > food borne botulism

2. Spores ingestion e.g Honey > germinate in the gut > toxin production > *infantile or (intestinal)* botulism

3. Spores contaminating wounds (e.g fractures, drug abusers)> germinate > toxin production > wound botulism

Clostridium botulinum

- Clinically (food borne and wound botulism):

✓ Incubation period 12-48hrs in food borne, longer in wound botulism (days – 2 weeks)

✓ Early: nausea, vomiting, weakness, dizziness but no fever

✓ Late: double vision, difficulty in swallowing, speaking and respiratory failure (descending motor paralysis)

- Infantile: weakness, altered cry, loss of appetite , loss of head control, Floppy child syndrome and sudden infant death syndrome

Clostridium botulinum

- Diagnosis:

- Isolating the organism or toxin from gastric aspirAtes, blood or stool

- Detecting Toxin in the food

- n.b: toxin-antitoxin approach?

- Alert the lab

Clostridium botulinum

✓ Treatment:

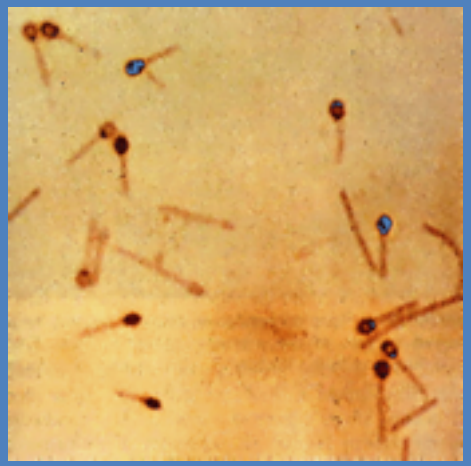
- Gastric wash
- Antitoxin
- Supportive: ICU and respiratory support,
- In Wound botulinum: antitoxin + cleaning and debridement plus antibiotics (metronidazole and penicillin) to reduce bacterial load

✓ Prevention:

- Proper cooking and heating of food?
- Avoid suspicious canned food
- Proper processing, preservation and canning of food
- vaccine

Clostridium tetani

- Widely distributed in the environment and in the soil
- Gram positive, motile anaerobic rods (GNR in old culture)
- β-Haemolysis when grown on blood agar
- grow well in cooked meat broth
- Spore forming: round terminal (drumstick, tennis racket)



Clostridium tetani

- Produce two plasmid coded exotoxins:

1. Tetnospasmin:

- Neurotoxin
- Heavy (binding) and light chain (neurotoxic part)
- One antigenic toxin

2. Tetanolysin (haemolysin): pathogenesis not clearly known but ? RBCs haemolysis

Clostridium tetani

- Pathogenesis:

Local secretion of the toxin > binding to the presynaptic

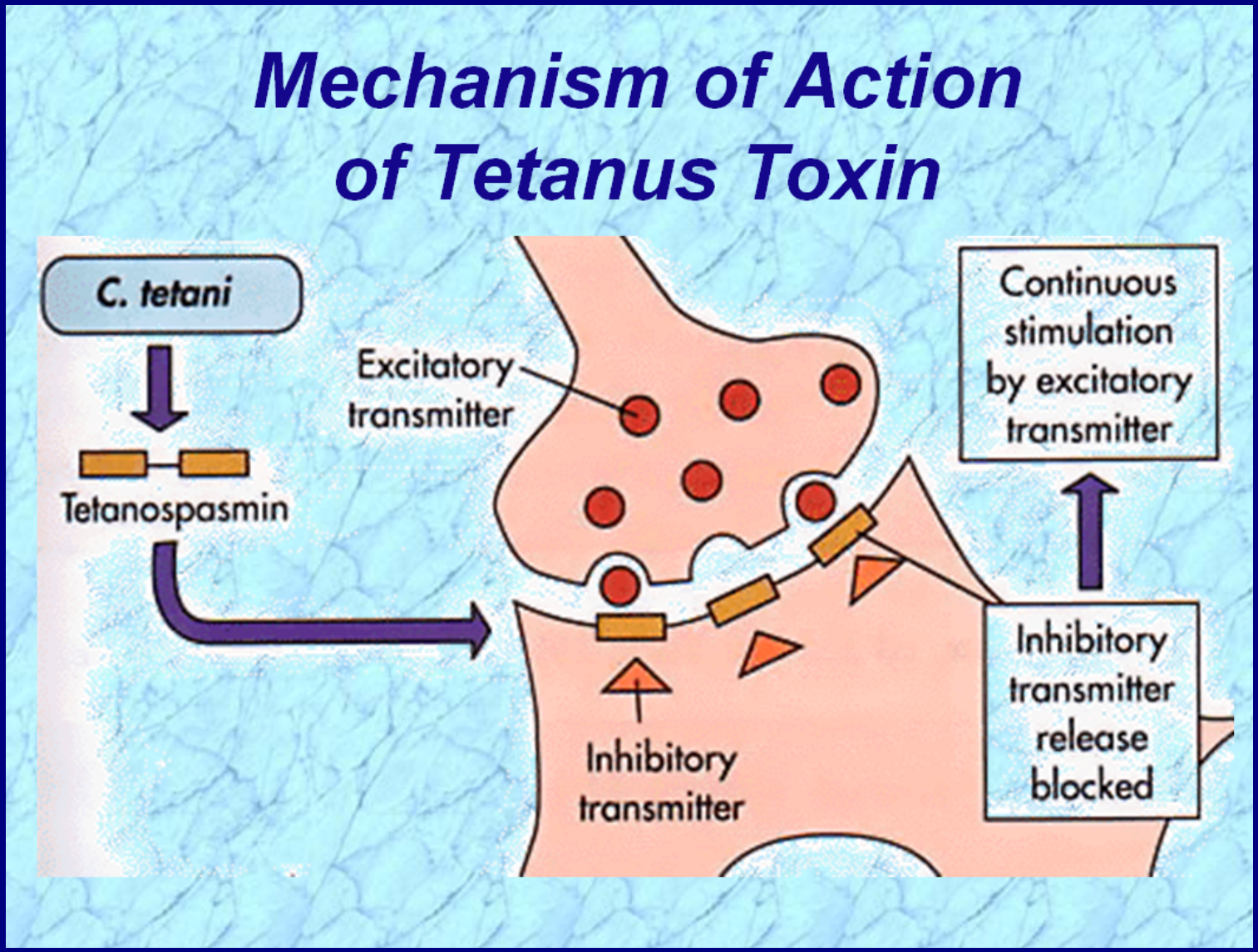
neurons (heavy chain) > retrograde diffusion of the light chain

to the spinal cord > inhibition of the inhibitory neurotransmitter

gamma aminobutyric acid (GABA) > loss of inhibitory action on

motor and autonomic neurons> uncontrolled muscle contractions (spasms) > Spastic paralysis

Clostridium tetani / pathogenesis



Clostridium tetani

✓ Clinically (tetanus):

- Mode of transmission:

- Spores > wound contamination(low oxygen) > germination to bacilli that secrete the toxins
- Incubation period: 3days – 3 weeks

✓ Source:

- Infected wound and abscesses (~65%), which often is minor (eg, wood or metal splinters, thorns...)
- Chronic skin ulcers are the source in approximately 5% of cases
- in the remainder of cases, no obvious source is identified (cryptogenic)

Clostridium tetani

1. Local: muscles spasm and pain at/near injury site

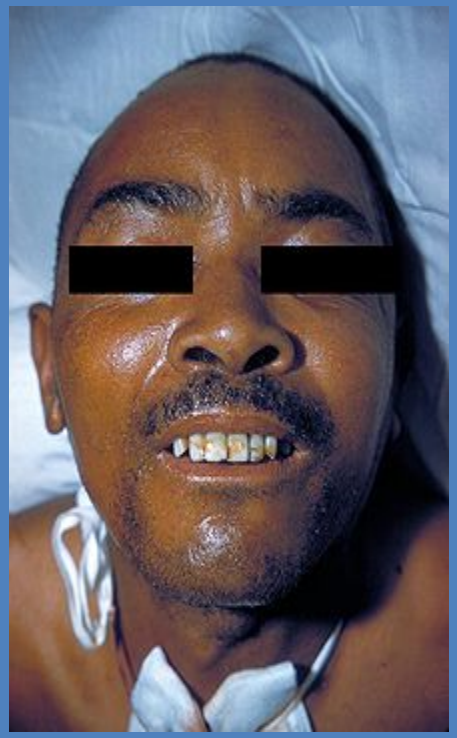
2. Cephalic:

- Following head trauma for example
- Localised picture that may progress to generalised
- cranial nerves palsy (7^{th} cranial nerve is commonly involved)

3. Generalised:

- Trismus (locked jaw): may bite the tongue
- Opisthotonus: flexion and adduction of the arms, clenching of the fists, extension of the lower extremities

Clostridium tetani



Clostridium tetani

3. Generalised cont'd:

- Risus sardonicus (sardonic grin): abnormal, sustained spasm of the facial muscles that appears to produce grinning or the scornful smile of tetanus
- spasm is stimulated by noise and light
- the patient is afebrile
- Meningitis, seizures and coma

Clostridium tetani

3. Generalised cont'd:

- During these episodes, patients have intact sensation and feel severe pain
- The spasms can cause fractures, tendon ruptures
- Arrhythmia, tachycardia and respiratory failure

Clostridium tetani

- Other forms tetanus:

✓ Infantile:

- Following umbilical cord contamination
- Develops within the first week to spastic Paralysis and is usually fatal

✓ Otogenic tetanus:

- source is from external auditory meatus (piercing, cleaning)

Clostridium tetani

Diagnosis:

1. Clinical (mainly):

- ✓ Sign and symptoms
- ✓ Vaccination history (part of the national childhood program)
- ✓ History of a trauma

2. Wound smear staining and culture: may help

3. Toxin-antitoxin test in mice : main lab. line

Clostridium tetani

- Treatment:
- Wound debridement
- Treat in In a dark quite room in ICU
- Sedation, Muscle relaxant (e.g diazepam) and artificial ventilation
- Antibiotics:

✓ may be given to kill any vegetative forms

✓ metronidazole

- Tetanus immunoglobulin (TIG) single IM dose
- Vaccinate if no history of vaccine or unknown or if the patient received incomplete vaccine doses in the past

Prion diseases
proteinaceous infectious particles

Main properties:

- Prion proteins normally found human brain PrP^{c}
  - PrP^{c} is protease sensitive and found on cell surface
  - Its function is unknown

- Prion disease caused by accumulation of abnormal prion protein called PrP^{sc}
  - Resistant to protease and found intracellularly

- Change of PrP^{c} to PrP^{sc} can be due to genetic, infectious or sporadic reasons

Prion diseases

- Accumulation of PrP^{sc} Occurs in human and animals causing spongiform encephalopathies
- These proteins has no nucleic acid
- Highly resistant to heat and disinfectants
- Sensitive to sodium hydroxide and 134C moist heat autoclave 5 hrs
- No immune response is generated to these proteins

Prions

Pathology:

- PrP^{c} is enzyme sensitive and has no tendency to accumulate
- while the PrP^{sc} is the opposite
- Accumulating PrP^{sc} is toxic to the brain > encephalopathies
- Degenerative changes in the brain characterised spongiform changes, vacuoles and amyloid plaques

Transmission:

- Ingestion
- Iatrogenic e.g blood transfusion, dura mater transplants and surgery (brain, tonsils, appendix and spleen)

Prions / clinically

1. Sporadic: Creutzfeldt – Jakob disease: 85% of cases

- Sporadic due to PrP^c spontaneous genetic mutation
- 1 case/million case, middle age and elderly (50-70 y)

- Rapidly progressive dementia and myoclonus
- Death in about 6months – 2 years following symptoms development

Prions

2. Acquired:

A. New Variant CJD (Bovine spongiform encephalopathy, mad cow disease):

- Reported in UK in 1996
- Ingestion of infected cattles
- Affected young age group ~ 27 years on average
- Symptoms:

Psychiatric > cerebellar symptoms > dementia

B. Iatrogenic: dura matter and cadaveric growth hormone transplants, blood transfusion, contaminated instruments....

C. Kuru:

- In New Guinea people
- Transmitted by eating the viscera and brains of relatives
- After a long incubation period >fatal cerebellar syndrome
- Ataxia and dementia

3 . Inherited:

A. Gerstmann - Straussler – Scheinker disease: AD inheritance

- Middle aged adults
- Cerebellar ataxia + spastic paraparesis
- Dementia lately

A. Fatal familial insomnia: AD inheritance

- Middle aged adults
- Thalamus is heavily involved
- Progressive insomnia and myoclonus
- Dementia is rare

Prions

Diagnosis:

- Clinically: dementia, myoclonus, ataxia
- EEG
- MRI
- Post-mortem

Treatment:

No specific treatment

The End