Summary

- Tetanus: symptoms caused by a powerful toxin from anaerobic bacteria
- Pathogenic organism present in wounds, umbilical stump infections
- Prevention by vaccination including pregnant women
- Clinical diagnosis
- Painful muscle spasms (spontaneous and after provocation), normal consciousness
- Treatment: wound care, antitoxin, anti-spasmodics, clear airways, supportive measures
- Avoid or treat complications

General

Tetanus is a disease caused by the toxin produced by an anaerobic bacterium: *Clostridium tetani*. This disease is completely preventable by vaccination therefore it is particularly tragic that is still occurs. The disease cannot be transmitted from human-to-human. *Clostridium tetani* is a strictly anaerobic Gram-positive rod-shaped bacterium, in cultures or in tissue it can be Gram-variable. It forms a characteristic spore at one end (exclamation mark, tennis racket). These spores are very resistant: they resist boiling, short autoclaving, alcohol and phenol. They are destroyed by autoclaving at 121°C for at least 12 minutes (better 15′). The bacterium occurs widely in nature for example in the soil and in the intestinal tract (especially of cattle and horses). Approximately 10% of people have C. tetani in their colon.

Neurotoxin

If the organism infects a wound where the oxygen concentration is low (interrupted vascularization, foreign body, tissue necrosis, umbilical stump) the bacterium can multiply. The bacterium itself is not invasive. The pathogenic organism produces a neurotoxin-tetanospasmin. This is released when the organism lyses. This protein is responsible for all the clinical manifestations of tetanus. The toxin is cleaved outside the cell by a bacterial protease into a heavy and a light chain. The toxin enters the neuromuscular junction. Once internalized, it migrates via the fast retrograde axonal transport pathway of the peripheral nerves towards the nerve soma located in the spinal cord. Another pathway which is hypothesised is via the lymphatics and the blood to the central nervous system. The neurotoxin inside the motor neurons translocates (crosses the synapse) to inhibitory

interneurons. There the toxin cleaves the protein synaptobrevin which is present on the presynaptic vesicles which contain the inhibiting neurotransmitters GABA and glycine. Due to the removal of synaptobrevin on the exterior of the vesicles the latter can no longer fuse with the synaptic membrane. Therefore the reflex arc cannot be inhibited. The consequence of the removal of the normal inhibition of the motor neurones is increased muscle tone at rest and tonic spasms. The toxin is also active on the sympathetic nervous system. The role of a second toxin- tetanolysin is still unclear.

GABA (gamma- Aminobutyric Acid)

Throughout the central nervous system, GABA is an inhibitory neurotransmitter. GABA receptors open channels for negatively charged chloride ions, hyperpolarizing the neuronal membrane and making it less likely that action potentials can be generated in output neurons.

Tetanospasmin is one of the most powerful toxins known to man (botulinum toxin is the undisputed leader). The toxin is present in the body at such low doses that it does not trigger an immunological response. **Tetanus can therefore be contracted more than once**. That is one reason why people with clinical tetanus should still be vaccinated.

Most cases of tetanus occur after wounds (lacerations, bites, burns, pricks, IM injections, umbilical infections in neonates, infected abortions, a sand flea burrowing under a toenail, infected Guinea worm). Sometimes the focus is a middle-ear infection (otitis media with perforated ear drum). In 20 to 30% of tetanus patients no entry point or wound can be found.

Clinical aspects



Neonatal tetanus with opisthotonus. Photo Cochabamba, Bolivia



Tetanus, adult man. Notice the slight opisthotonus. Copyright ITM

The incubation period varies: the shorter it is the more serious the infection. Neonates who contract tetanus before they are 7 days old almost never survive. The incubation period varies between a few days and a few weeks. Three clinical forms can be distinguished:

Localized tetanus: rigidity and painful spasms in a group of muscles in the area of the wound, without general involvement. This form is rare. It is sometimes prolonged for months. The mortality rate is < 1%.

Generalized tetanus, including neonatal tetanus: first there is a short period of restlessness, irritability, dysphagia and sweating. Trismus frequently occurs (spasms of the masseter = jaw muscle). Patients are no longer able to open their mouths wide. Another name for tetanus is “lockjaw”, which refers to the trismus. If the spasms spread to the other muscles of the face a spastic grimace sets in: risus sardonicus (“bitter laugh”). The disease

typically descends; after the jaws and the face to follow the neck, back, abdomen and finally the extremities. Back muscle spasms lead to arching backwards (opisthotonus). Successive attacks of opisthotonus are characteristic. The spasms are very painful and last a few seconds to a few minutes. They can occur spontaneously or are elicited by all kinds of stimuli (sudden noises, touching, sudden bright light). Because the latter is a well-known phenomenon, the patients are sometimes placed in a dark room. This sometimes leads to insufficient nursing care with serious consequences. The body temperature, heart rate and blood pressure are variable because the autonomic nervous system is also affected. In most cases there is rather low to moderate fever but hyperpyrexic periods do occur.

Cephalic form: Occasionally a true cephalic form occurs, with symptoms affecting the head, throat and neck; while sparing the rest of the body.

Differential diagnosis:

Generalized tetanus

Bacterial meningitis and subarachnoidal haemorrhage: lumbar puncture

Epilepsy: no muscle rigidity between spasms, history of previous episodes

Extrapyramidal reactions and dystonias while on neuroleptics, such as phenothiazines e.g. chlorpromazine (Largactil®) or metoclopramide (Primperan®).

Cerebral malaria: thick film test, no muscle rigidity between convulsions

Acute strychnine poisoning resembles tetanus very closely, and an old proposed name for strychnine was “tetanine”. This bitter colourless alkaloid is obtained from the ripe seeds of *Strychnos nuxvomica* and related plants, such as Saint Ignatius beans (*Strychnos ignatia*) and snake wood (*Strychnos colubrina*). The plant seeds are sometimes used in traditional medicine (e.g. in Cambodia). It is a competitive antagonist of glycine, an inhibitory neurotransmitter. There are face spasms followed by hyperreflexia in the legs and arms. This is followed, a little later by painful generalised convulsions, triggered by sudden sounds or stimuli. The patient may be conscious. Finally breathing difficulties and coma follow. Upon

death, rigor mortis sets in very quickly. If the patient survives recovery is fairly quick unlike tetanus.

Hypocalcaemic tetany after accidental parathyroidectomy or in primary hypoparathyroidia is rare. The parathyroid glands secrete parathyroid hormone which increases the concentration of calcium in the blood. If there is a shortage of parathyroid hormone, the calcium levels in the blood fall and convulsions may occur. There may be spasms of the hands and feet as well as tingling around the mouth. Trismus is rare. Chvostek's and Trousseau's sign may be present.

Rabies: hydrophobia, periods of confusion, brain stem symptoms and cranial nerves being affected.

Trismus

- Dental abscess, peritonsillar abscess
- Pharyngeal diphtheria
- Fracture of the mandible
- Mumps

Diagnosis

The diagnosis is purely clinical. Repeated tonic spasms with muscle rigidity between the convulsions are typical. Spasms can be triggered by sudden stimuli: e.g. clapping the hands. The patient is fully conscious. *Clostridium tetani* can be found in wounds in less than 30% of cases, but a microbiological diagnosis via culture is less important than making a clinical diagnosis. The cerebrospinal fluid is normal.

Treatment

Tetanus is a disease which can drag on for weeks. There is high mortality. Treatment consists mainly of neutralising toxin and preventing convulsions and complications. Thorough cleansing of the wound and good nursing care are the most important factors in determining whether the patient survives or not.

1. The pathogenic organism, *Clostridium tetani,* has to be eradicated: by wound cleansing (hydrogen peroxide, povidone iodine [Iso-Betadine®], debridement) and penicillin G preferably IV, e.g. 1 to 12 million units per day. However, it is possible that penicillin G may act on GABA transmission and exacerbate the toxin's effect. Therefore the use of penicillin is controversial. Metronidazole is sometimes recommended instead.
2. The toxin which is still circulating must be neutralised with antitoxin. Human hyperimmunoglobulin is best: one single IM injection of 3000 to 6000 IU in two different sites (or 10,000 to 50,000 IU hyperimmune horse serum). Sometimes lower quantities are recommended. Human antiserum has a half-life of 25-28 days therefore it must not be given repeatedly. The half-life of horse antiserum is somewhat less than 2 weeks. Toxin which has already bound to nerve cells, cannot be removed and is responsible for the repeated spasms. Some guidelines use tetanus immunoglobulins intrathecally.
3. The infection does not produce any immunity so that the patient must also be vaccinated. The vaccine must not be mixed with gammaglobulins and must be injected at another site.
4. Prevention of muscle spasms is important because the spasms are very painful, and they interfere with breathing. They can lead to gastric reflux with aspiration pneumonia. The repeated violent convulsions can even result in patients breaking their own bones. Diazepam (Valium®) is better than barbiturates and is often used as the drug of first choice. Sometimes very large quantities have to be given (50 to 500 mg/day). Respiratory depression can occur.Midazolam (Dormicum®) is an alternative. In the case of depression of the central nervous system, flumazenil (Anexate®) can be used as an antidote. Dantrolene (Dantrium®) can be used but it is very expensive. Chlorpromazine (Largactil®) is also useful. Baclofen (Lioresal®) is a GABA B receptor agonist that inhibits pre-synaptic acetylcholine release and synaptic medullar reflexes (i.e., lowers excitability of motor neurons), which results in an antispastic action. It is rarely available in low resource setting. If possible, baclofen can also be administered intrathecally.
5. Trismus, dysphagia, laryngeal spasms, respiratory muscle spasms, gastric reflux and sedatives can lead to pulmonary complications. Aspiration of secretions to clear the airway is necessary. Oxygen will often be given. Sometimes tracheostomy (severe laryngeal spasms) is performed. The indications for tracheostomy are acute airway obstruction due to laryngeal spasms that interfere with respiration, or to facilitate mechanical ventilation. If the means are available, curare (muscle relaxant, e.g. pancuronium = Pavulon®, vecuronium) and mechanical ventilation can be used.
6. The use of magnesium sulfate infusions in the management of tetanus enables one to

minimize sedation and reduce the need for mechanical ventilation, and thereby greatly simplifying the care of the tetanus patient. Magnesium is also able to minimize sympathetic overactivity associated with tetanus. Furthermore, magnesium sulfate is already a well-known entity due to its extensive use in the management of pregnancy induced hypertension. As a guide line for an adult, a loading dose of 5 gram is given, followed by 2-3 gram per hour afterwards.

7. The patient must be regularly turned to prevent pressure sores. The risk of pulmonary embolism decreases with subcutaneous heparinisation. Low-molecular heparin can be given prophylactically, but this is often not available in the tropics. Feeding is performed mainly via a thin flexible nasogastric tube (the patient cannot eat for weeks), his is sometimes overlooked. Urinary catheterisation is necessary to prevent urine retention.
8. Septicaemia occurs frequently in neonatal tetanus (umbilical stump as the point of entry) and must not be ignored. In third world countries, it is not unusual for the umbilical stump to be covered with various contaminated herbs, animal droppings or fats.
9. Beta-blockers such as labetalol can be administered in cases of excessive sympathetic tone. In the case of hypotension, IV fluid and vasopressors should be administered if available.

Example of “Adult tetanus protocol”

1. Start metronidazole intravenously 500mg three times a day.
2. Give tetanus human immune globulin IM 3,000-6,000 iu if available. If not available Equine ATS 10,000 iu IM.
3. Admit ICU, commence oxygen, IV access and monitoring.
4. Alert surgeon to do radical debridement. Nasogastric tube may be passed during surgery.
5. Slow loading dose diazepam IV to control spasms. Up to about 40mg may be required. Give a loading dose of 5g magnesium sulphate slowly over 20 minutes IV.
6. Start diazepam 10mg 6 hourly and increase to hourly if required. Titrate to symptoms.
7. Start magnesium 2.5g IV 2 hourly and increase to hourly if required. Titrate to symptoms. Stop diazepam if symptoms controlled by magnesium alone.
8. Phenobarbitone up to 200mg IV twice a day for breakthrough spasms using 50mg doses.
9. Tracheostomy if airway compromised by above treatment.
10. Intermittent positive pressure ventilation with muscle relaxants if respiration compromised by treatment or uncontrolled spasms.

Prognosis

Incubation period < 7 days:

1. The course of the disease is always very serious.
2. The interval between the first symptoms and generalized spasms is 3 days or less.
3. Mortality rate > 80 %

Incubation 7 to 10 days:

1. Moderately severe course with the symptoms developing over 3 to 6 days.
2. The mortality rate varies from centre to centre.

Incubation > 10 days:

1. Milder course with the usual symptoms setting in slowly.
2. Generalized convulsions are sometimes absent.
3. If a baby survives neonatal tetanus there is an increased risk of permanent brain damage, with behavioural and developmental problems as well as difficulties with fine motor movements.

Prevention

In the case of a wound which is likely infected with *C. tetani*, prior to symptoms development; in addition to wound care and tetanus vaccination, human hyperimmunoglobulins are given intramuscularly, i.e. 250 to 500 IU once only. Hyperimmune horse serum can be used but this sometimes leads to anaphylactic reactions and serum sickness. Tetanus toxoid (toxin inactivated by formalin) is used for vaccination. The vaccine is administered intramuscularly on 3 occasions with a minimum interval of one month between each injection. There is a booster after 1 year and then every 10 years (or after 5 years if injured). It is best if children are vaccinated at the age of 2, 4, 6 and 15 months of age. This series is completed with a dose between 4 and 6 years. Additional boosters are given every 10 years after that. A serum antitoxin concentration of 0.01 IU/ml is regarded as protecting against tetanus. This determination can only be carried out in a few laboratories.

The antibodies (particularly subclass IgG1) cross the placenta from mother to child and protect the neonate from neonatal tetanus. These antibodies gradually disappear from the child's blood over the following months. Vaccination of the mother is therefore part of the prenatal consultation. The vaccine is very efficient and very safe. It is part of the EPI (extended programme of immunization) of the WHO.