Tetanus: The Forgotten Disease

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Introduction

Tetanus was well known to the ancient physicians of Egypt and Greece, but since institution of the active immunization in 1940, it has become an old forgotten disease in developed countries.[1] Tetanus is a nervous system disorder characterized by prolonged contraction of the skeletal muscles. The disease is caused by tetanospasmin, a neurotoxin produced by the anaerobic bacterium *Clostridium tetani.*

Case Report

A 74-year-old Caucasian female presented to the emergency department complaining of trismus. The patient had not been evaluated by a physician for several years. Her symptoms started 10 days prior with difficulty opening her mouth, generalized muscle stiffness, and episodic muscle spasms. She denied fever and chills, was not taking any medications, and had no history of alcohol or illicit drug use. She did not remember ever receiving tetanus vaccination.

On physical examination, the patient was unable to open her mouth more than 1 cm and the masseter muscle was contracted. She had a generalized increase in muscle tone and episodic painful muscle spasms involving the entire body. Multiple scars in different healing stages over the lower extremities had been caused by scratches from her 13 cats.

The diagnosis of generalized tetanus was suspected. Five hundred units of human tetanus immunoglobulin were given intramuscularly and active immunization was started. Although there was no active wound infection, the patient was started on intravenous metronidazole. Muscle spasms and rigidity were controlled with a scheduled dose of intravenous diazepam. Over the next three weeks, the patient's symptoms gradually improved, and she was discharged to a skilled nursing facility.

Epidemiology

The incidence of tetanus in developed countries dropped dramatically since 1940 mainly due to the widespread use of active immunization.[1] Better hygiene and wound care also have played a major role. The annual incidence of tetanus in the US has fallen from 4 to 0.2 per million since 1947.[1] The decline in incidence was accompanied by a decrease in mortality from 50 to 30%.

Between 1998 and 2000, the annual incidence of tetanus was 0.16 cases/million representing an average of 43 cases per year.[2] The majority of cases were in patients older than 60 years, reflecting the waning of immunity with age or inadequate immunization of the elderly.[1] Injection drug abuse and the increase of non-immunized immigrants are responsible for most cases of tetanus in younger individuals aged 25 to 59. According to the CDC[2], 15% of cases of tetanus in the US occurred in intravenous drug users.

Acute injuries account for 70 to 80% of US cases; 23% of cases are associated with chronic decubitus ulcers, gangrene, burns and abcesses.[1] About 7% of cases have no apparent source. Neonatal tetanus is rare in the US.[1,2]

Tetanus is common in developing countries. The worldwide incidence is about 1,000,000 cases per year.[3,4] It is a major cause of death especially in neonates. Tetanus accounted for 300,000 deaths in 2000, including 200,000 neonatal deaths.[5]

Pathogenesis and Pathology

Clostridium tetani is an obligatory gram positive anaerobic bacillus. The bacteria are usually found in contaminated soil and animal gut in the sporiform phase. When these spores contaminate a wound, they germinate under anaerobic conditions, transform into a rod-shaped bacterium, and produce tetanospasmin. Tetanospasmin is an exotoxin produced by mature bacteria, then cleaved intracellularly into light and heavy chains before exocytosis. The heavy chain appears to mediate binding to cell surface and transport proteins, while the light chain is responsible for the clinical manifestations of tetanus.[1]

After its excretion, tetanospasmin gains entry into the central nervous system (CNS), both locally and distally, via the presynaptic terminals of lower motor neurons. Tetanospasmin is transported intra-axonally in a retrograde fashion to the cell body, the ventral horns of the spinal cord, and to the motor nuclei of the cranial nerves where it exerts its major pathogenic action. After reaching the spinal cord and the brain stem, tetanospasmin binds tightly and irreversibly to specific receptors, inhibiting the release of inhibitory neurotransmitters (glycine and γ-amino-butyric acid) from presynaptic inhibitory neurons.

The net effect is the disinhibition of motor excitatory neurons resulting in increased muscle tone and painful spasm. The autonomic nervous system also is affected, manifested by a hypersympathetic state due to failure to inhibit the adrenal release of catecholamine. Tetanospasmin interferes with pre-synaptic acetylcholine release at the neuromuscular junction and disinhibits sympathetic reflexes at the spinal level.[1] The inhibitory effect of tetanospasmin is irreversible. Recovery requires the growth of new axonal nerve terminals in 4 to 6 weeks. Clostridium tetani produces another toxin called tetanolysin that apparently has no pathogenic role.[1]

Clinical Features

The incubation period of tetanus usually lasts between 3 and 21 days with a range of one day to several months.[1] A correlation exists between the distance of the injury from the CNS and the duration of the incubation period.[1,5] The closer the distance, the shorter the incubation period. Both the incubation period and the time of onset (time from the first symptom to the first generalized spasm) inversely correlate with prognosis.[1]

Tetanus has four clinical forms: generalized, localized, cephalic, and neonatal. Generalized tetanus is the most common and severe. The generalized form typically starts with spasm of the masseter muscles, causing trismus or "lockjaw" and increased tone of the orbicularis oris resulting in the characteristic "risus sardonicus". The patient experiences diffuse spasms involving muscle groups in the neck, back, abdomen, and extremities. These spasms are painful, intermittent, and unpredictable. They often are triggered by noise and light.

Patients with generalized tetanus typically have symptoms of autonomic overactivity that manifest as sweating, tachycardia, cardiac arrhythmia, labile hypertension or hypotension, and fever.

Respiratory muscles also are affected causing periods of apnea. During generalized tetanic spasms, patients characteristically clench their fists, arch their back, flex their arms while extending their legs, and become apneic.[1] Death is due to respiratory failure or to autonomic dysfunction. Recurrent tetanus may occur if the patient is not immunized since the infection does not confer immunity. Recovery is typically 2 to 6 weeks.

Localized tetanus is usually a prodrome of the generalized form. It presents with localized rigidity and spasm of a muscle group near the site of injury. Subsequently, patients develop generalized tetanus. In some cases, localized disease reflects partial immunity with resolution of the spasms without generalization.[6] Cephalic tetanus is a form of localized tetanus involving the cranial nerves in a patient with head and neck injuries.[1]

Neonatal tetanus is related to the inadequate use of aseptic techniques in non-immunized mothers. It usually occurs within 14 days after birth.[1,7] Infants present with generalized weakness and failure to nurse, followed by rigidity and spasms. Mortality exceeds 90%. Apnea and sepsis are the leading causes of death.

Diagnosis

The diagnosis of tetanus is based on clinical symptoms and a high index of suspicion in susceptible individuals.[1] Anaerobic cultures from the wound are usually negative. A positive culture does not confirm the diagnosis. Anti-tetanus antibodies are undetectable in the majority of patients with tetanus. However, the presence of antibodies at low titer does not confer immunity and cannot be used to rule out the disease. Electroencephalography and electromyography can be helpful in ruling out other conditions.

Differential Diagnosis

Strychnine poisoning may produce a clinical syndrome similar to tetanus. Toxicologic screen of urine and blood should be performed if a suspicious injection is suspected or the history is not typical for tetanus (e.g., no injury or adequate immunization). The treatment of tetanus and strychnine poisoning is similar.

Trismus due to dental infection may be confused with cephalic tetanus. Drug induced dystonia and malignant neuroleptic syndrome can mimic tetanus.

Treatment

The treatment of patients with tetanus requires a multidisciplinary approach in the intensive care unit.[1] The mainstay of treatment consists of eliminating the source of toxin production, neutralizing unbound toxin, and managing symptoms and complications.

Halting toxin production

Wound debridement is important to eliminate the source of toxin production. All foreign bodies, including spores and necrotic tissue, should be removed. Metronidazole and penicillin G are the drugs of choice, but studies have shown better outcomes with metronidazole.[1,8] Intravenous metronidazole should be given initially at a dose of 15mg/kg followed by 20 to 30 mg/kg/day intravenously for 7 to 14 days or until there is no visible sign of active local infection.[1] Alternatives include cefazolin, cefuroxime, and ceftriaxone.

Neutralizing of unbound toxin

Tetanospasmin is bound irreversibly to tissues and only unbound toxin is available for neutralization. Passive immunization with human tetanus immune globulin (HTIG) shortens the course of tetanus and improves survival. A dose of 500 units of

HTIG should be given intramuscularly as soon as the diagnosis of tetanus is considered.[1,9] The use of intrathecal HTIG is not indicated.[1]

Management of muscle spasms

Generalized spasms are life threatening. Patients should be placed in a quiet dark room to avoid provoking muscle spasms. Spasms can cause exhaustion when severe.

Benzodiazepines are the mainstay in the symptomatic therapy of tetanus. They are usually effective in controlling muscle spasms, and patients may benefit from their amnestic effect. These drugs are gamma-aminobutyric acid (GABA) agonists. They have the potential of antagonizing the effect of the toxin.

Treatment with diazepam, lorazepam, and midazolam appear to be equally effective. Oral administration of these drugs is possible, but some patients do not absorb the drugs well and develop gastrointestinal motility disorders. Diazepam 10 to 30 mg intravenously is the usual starting dose. The intravenous formulation of diazepam and lorazepam contains propylene glycol that can cause lactic acidosis at high doses. Intravenous midazolam does not contain propylene glycol, but must be given as a continuous infusion of 5 to 15 mg/hour.

Intravenous propofol infusion is effective in controlling spasms and rigidity. It is expensive and associated with lactic acidosis, hyper-triglyceridemia, and pancreatic dysfunction.[1]

Neuromuscular blocking agents can be used in severe cases. Pancuronium (intermittent injection) and the shorter acting vancuronium (continuous injection) are usually used. Vancuronium is preferred over pancuronium because of the worsening of autonomic instability observed with the latter. Both agents should be used cautiously and the patient should be sedated adequately. These agents should be stopped daily to assess the patient's progress, and to observe for possible complications.

Intrathecal baclofen was found to control spasms and rigidity in a few small studies.[10]

Management of autonomic instability

Magnesium sulfate is effective in the treatment of autonomic dysfunction in patients with tetanus.[1,11] It also has a potential role in controlling muscle spasms. Magnesium sulfate blocks cathecholamine release from the nerves and reduces receptor responsiveness to cathecholamine.

Labetolol (0.25 to 1 mg/min) could be used because of its dual alpha and beta blocking properties.[1] Beta blockade alone should be avoided because the resulting unopposed alpha effect may produce severe hypertension and even death. Other useful agents include morphine sulfate by continuous intravenous infusion, atropine, and clonidine.

Supportive Care

Patients with tetanus are at risk of respiratory failure and aspiration. Many require endotracheal intubation to maintain adequate ventilation and preserve the airway.[1] Early tracheostomy usually is preferred in patients with tetanus who develop respiratory failure because of the likelihood of prolonged mechanical ventilation.

Nutritional support should be started as soon as possible because energy demands and protein requirements are very high. Physical therapy should be started as soon as the spasms have ceased.

Active Immunization

Tetanus is one of the rare bacterial infections that do not confer immunity following recovery. All patients with tetanus should receive active immunization with three doses of tetanus and diphtheria toxoids spaced at least two weeks apart, with

the first dose administered upon diagnosis. It should be presumed that patients who are inadequately immunized to tetanus are inadequately immunized to diphtheria as well.[12] Subsequent doses should be given at 10-year intervals throughout adulthood.

Prophylaxis

Tetanus is a preventable disease.[1] A series of three monthly intramuscular injections of tetanus toxoid provides adequate immunity for at least 5 years. Patients younger than 7 years of age and those never immunized to pertussis should receive the combined diphtheria-tetanus-pertussis vaccine (Tdap). Tetanus-diphteria (Td) booster injections are indicated every 10 years. Mild reaction to tetanus toxoid is common including local tenderness, edema, and low grade fever. Severe reactions are rare. Guillain-Barre syndrome was linked to tetanus toxoid in some reports but this was not confirmed in subsequent epidemiologic analysis.[1]

The CDC[13] has recommended administering tetanus toxoid-containing vaccine and tetanus immune globulin (TIG) as part of standard wound management to prevent tetanus (see Table 1). Tdap is preferred to Td for adults vaccinated less than five years earlier who require a tetanus toxoid-containing vaccine as part of wound management and who have not received Tdap previously. For adults previously vaccinated with Tdap, Td should be used if a tetanus toxoid-containing vaccine is indicated for wound care. Adults who have completed the 3-dose primary tetanus vaccination series and have received a tetanus toxoid-containing vaccine less than five years earlier are protected against tetanus and do not require a tetanus toxoid-containing vaccine as part of wound management.

Persons with unknown or uncertain tetanus vaccination histories should be considered to have had no previous tetanus toxoid-containing vaccine. Persons who have not completed the primary series might require tetanus toxoid and passive vaccination with TIG at the time of wound management (see Table 1). When both TIG and a tetanus toxoid-containing vaccine are indicated, each product should be administered using a separate syringe at different anatomic sites. Adults with a history of Arthus reaction following a previous dose of a tetanus toxoid-containing vaccine should not receive a tetanus toxoid-containing vaccine until at least 10 years after the most recent dose, even if they have a wound that is neither clean nor minor. In all circumstances, the decision to administer TIG is based on the primary vaccination history for tetanus (see Table 1).

Table 1. Recommendation for use of tetanus prophylaxis in wound management.

Immunization with tetanus toxoid	**Clean, minor wounds**		**All other wounds**	
	Tetanus toxoid	Immunoglobulin	Tetanus toxoid	Immunoglobulin
Unknown or less than three doses	Yes	No	Yes	Yes
Three or more doses	No, unless >10 years since last dose	No	No unless > 5 years since last dose	No

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