

Tetanus: Forgiven, Not Forgotten

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Abstract

Tetanus is an illness that is still prevalent although the incidence has markedly decreased largely due to immunisation programmes. The latest four cases managed at St. Luke's hospital over 2001-2002 are presented. All of these patients survived. We give an overview of the illness and discuss the cases and management. The potential benefit of using dual antibiotic therapy is questioned.

Introduction

The incidence of tetanus has been decreasing in the developed world mainly due to effective immunisation programmes. As a result, physicians are less exposed to the features of this serious, potentially fatal illness. However, sporadic cases serve to raise awareness that although this disease has been largely overcome mainly through preventative methods, it is still around and an index of suspicion has to be maintained in patients presenting with the characteristic features. Here we describe four cases to demonstrate the features and management issues that may arise in these cases.

Keywords

Tetanus, *clostridium tetani*, benzyl penicillin, metronidazole, magnesium sulphate

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Case 1

LA, a previously healthy 63-year-old male, was referred with an inability to swallow liquids and solids, followed by a 24 hr history of inability to open and close his mouth. Symptoms started insidiously and progressed slowly. He had a history of a traumatic nail puncture wound in the right foot 19 days prior to presentation. He had been treated at a health centre and was given anti-tetanus toxoid (ATT) and antibiotics. The patient stopped his antibiotics after 5 days of treatment. On examination, a small wound in the right foot, 5cm in diameter and 2-3cm deep, was present. He had neck stiffness and trismus of the jaw. There was no evidence of cardiovascular or respiratory failure. A diagnosis of tetanus was made and he was admitted to the Intensive Care Unit (ICU) and treated with benzyl penicillin and metronidazole. He also received antitetanus immunoglobulin (ATIG), his wound was debrided and he was placed on a magnesium sulphate infusion. After 4 days on ICU, the patient had to be ventilated because of progressive respiratory failure and subsequently required a tracheostomy. His stay on ICU was largely uneventful apart from supra-infection with multiresistant *Staphylococcus aureus* (MRSA). After 29 days the muscle relaxants were stopped. He was transferred to the Infectious Disease Unit (IDU) after 33 days and discharged home on day 37.

Case 2

HB, an 82 year old well preserved male with a history of asthma, adenocarcinoma prostate and nephrectomy due to pyonephrosis, presented with a 3 day history of difficulty opening mouth which initially started after an argument with his wife. He was seen by a dental surgeon and later by an Ear, Nose and Throat (ENT) surgeon and eventually admitted to the ENT ward. He had a history of an injury to the right popliteal fossa 1 week before. On being seen by the Infectious Disease team, he had lockjaw, was cyanosed and had basilar creps. He had no focal neurological signs. A clinical diagnosis of tetanus was made and he received ATIG 10,000 U, intravenous benzyl penicillin and metronidazole. Since he was in respiratory failure from pulmonary oedema, he was immediately intubated and ventilated. In intensive care, he was treated with the above antibiotics as well as inotropes and a magnesium infusion. Complications included nosocomial infections which were treated, supraventricular tachycardia and limb oedema.

Episodic spasms were controlled with adjustment of sedation and magnesium infusion. After 39 days on intensive care, he was transferred to the IDU from where he was discharged home.

Case 3

CP, a 66-year-old male hypertensive was seen at ENT Accident and Emergency (A&E) Department complaining of a 3 day history of difficulty in opening his mouth, and 1 day history of problems with swallowing. 1 week before he had injured his left big toe while gardening with subsequent avulsion of his toenail. On examination, the patient had trismus, jaw opening was limited to 1cm, and lateral jaw movements were limited. The left big toenail had been avulsed but there was no surrounding cellulitis. He had last taken Anti tetanus toxoid about 20 years before. He was admitted to the IDU and started on benzyl penicillin and metronidazole intravenously. ATT cover was given and later antitetanus immunoglobulin. The day after admission he was feeling worse with increasing difficulty with opening his mouth and swallowing, choking on oral fluids and difficulty moving his tongue, talking and keeping his eyes open. He was transferred to intensive care and observed but 2 days later developed respiratory distress and was ventilated, sedated and muscle relaxed. During this time he was being treated with the above antibiotics, and magnesium infusion. He was also treated for nosocomial pneumonia. After 40 days he was transferred from Intensive Care back to the IDU where he was discharged well and independent a few days after.

Case 4

RG, a 76 year old lady was referred from A&E to ENT for assessment of a 7 day history of difficulty swallowing. On examination, she had limited tongue movements and facial features suggestive of trismus, together with an inability to open the mouth fully. Flexible laryngoscopy showed a normal larynx. Some swelling of the face was present and superior vena cava (SVC) obstruction was initially entertained. She had a history of walking in her fields with some minor abrasions on her legs. An SVC venogram was however negative. She was started on co-amoxiclav and hydrocortisone and an Infectious Disease consultation asked for. The picture was not any clearer and a spatula test done and was negative repeatedly. The antibiotic spectrum was broadened and metronidazole added. Within the next two days, the situation was slightly worse, and the patient was also complaining of back pain, but no spasm. A clinical diagnosis of tetanus was made and the patient transferred to the ICU. She was given ATIG and benzyl penicillin was added. She was started on a magnesium infusion and her superficial wounds debrided. She managed to maintain the airway and the spasm in her mouth got better. Swallowing improved and she was transferred to the IDU after seven days, where she was gradually weaned off magnesium. On day 18 in hospital, her antibiotics were stopped and she was discharged home to continue a course of ATT.

Up to the time of this submission, two further cases were being managed at St Luke's Hospital and were doing well out of intensive care after prolonged supportive measures including mechanical ventilation in the ICU.

Overview

The first description of tetanus dates back to 460-377 BC by Hippocrates and Egyptian physicians. It was well known to ancient civilisations who recognised the relationship of injury to fatal spasms. The name derives from the Greek *Tetanos*, to stretch.

Carle and Rattone first produced tetanus in animals by injecting them with pus from a fatal human tetanus case in 1884. During the same year, Nicolaier produced tetanus in animals by injecting them with samples of soil. In 1889, Kitasato reported that the toxin could be neutralized by specific antibodies. In 1897, Nocard demonstrated the protective effect of passively transferred antitoxin, and passive immunization in humans was used during World War I. Tetanus toxoid was developed by Descombey in 1924, and the effectiveness of active immunization was demonstrated in World War II. Many of the immunisation programmes started after this time.

Aetiology

This illness is caused by an exotoxin called Tetanospasmin, produced by *Clostridium tetani*, anaerobic gram-positive rods which can form spores with the characteristic drumstick appearance. Spores are found in soil, dust, and animal faeces, and may persist for months to years. They are very resistant to environmental extremes and chemical agents. *Clostridium tetani* spores enter the body, usually via an open wound, the spores germinate, and toxins, including tetanospasmin, are produced, and disseminated via blood and lymphatics.

Pathophysiology

Tetanospasmin binds to receptors via pre-synaptic terminals of the lower motor neurone resulting in local failure of neuromuscular transmission. It travels up the axon to the cell body and diffuses to terminals of inhibitory cells, preventing transmitter release. It thus leaves motor neurons without inhibition and leads to unopposed muscle contraction and spasm. This may also result in seizures and autonomic nervous system dysfunction.

Clinical features

The incubation period varies between 3-21 days, averaging 8 days. Four types of clinical presentations can occur: generalised, local, cephalic and neonatal tetanus. Generalised tetanus is the most common form and usually starts with spasm of the masseter muscle. Neck rigidity, dysphagia and facial muscle involvement are also early features, the latter causing the *risus sardonius*. Progression occurs into generalised muscle spasms and tonic contractions, which can even cause fractures,

tendon ruptures and respiratory failure. Local tetanus presents with persistent muscle spasm in the muscles close to the injury. Patients with cephalic tetanus have cranial nerve palsies and this can follow head trauma or otitis media. Neonatal tetanus occurs in underdeveloped countries after contamination of the umbilical cord after delivery.

Differential diagnosis

The condition which may mimic tetanus is strychnine poisoning. Other conditions, which may cause trismus, include dental infections (note the second patient was referred to dentistry initially), encephalitis, local neoplasms and hysteria. Muscle dystonic reactions secondary to neuroleptics may also cause neck stiffness, but this usually includes lateral head turning which is rare in tetanus.

Epidemiology

In the year 2000, only 18 833 cases of tetanus were reported to the World Health Organization worldwide¹, but there was lack of data from many countries which are at greatest risk from this disease.² In Malta the annual reported number of cases of tetanus has been decreasing since the late 1970's (Figure 1). The figure of around 8 cases per year declined to about 1 case per year over the past 7 years (no cases in 1999). In 2003, however, there was an increase in trend with 3 cases being diagnosed. Current statistics indicate that the mortality rate varies from 6% to 60%, depending on severity. A shorter incubation period is associated with increased mortality, as is age more than 60 years.

Diagnosis

The diagnosis is made on a clinical basis. A bedside clinical test, called the spatula test can be used: this involves touching the oropharynx with a spatula which usually elicits a gag reflex and repulsion. The test is positive when the patient develops a reflex spasm of the masseters and bites the spatula. This test is said to have a 94% sensitivity and 100% specificity, and no adverse sequelae from this test have been reported.

Laboratory studies help to exclude other conditions. Strychnine levels in serum and urine help exclude toxicity. CSF studies are usually not necessary but would help to differentiate encephalitis. Although a serum tetanus antibody level of >0.01 U/ml is commonly cited as 'protective', there have been many case reports of disease in patients with antibody levels above this.³

C. tetani may be recovered from the wound in only 30% of cases. However, this can also be isolated from patients who do not have tetanus. Laboratory identification of the organism depends most importantly on the demonstration of toxin production in injected mice.

Management

Principles of management include support of the airway and control of spasms initially. This is done by ventilation, if

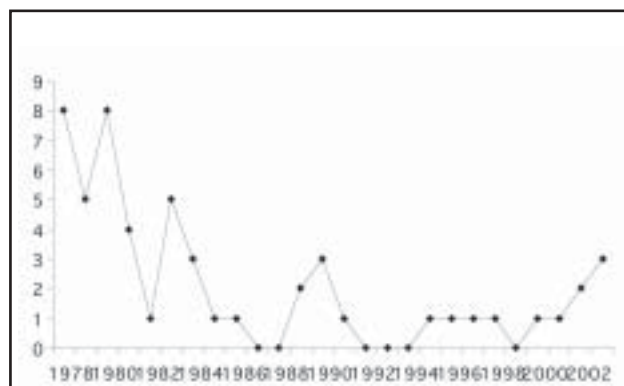


Figure 1: Annual number of reported cases of Tetanus: Malta 1978-2003

necessary, in an intensive care setting, and use of antispasmodic agents. The initial agents of choice would be the benzodiazepines, particularly diazepam or lorazepam. Other agents, which may be used, include midazolam, propofol, and intrathecal baclofen. Several studies have also demonstrated the benefit of magnesium infusion as an antispasmodic agent.⁴ This agent is especially important in resource poor areas, averting the need for mechanical ventilation.⁵ If control cannot be achieved by these agents, then neuromuscular junction blockade and ventilation will be necessary, whilst still maintaining an adequate dose of sedation.

Possible antibiotic treatments of tetanus include metronidazole and benzyl penicillin. Morbidity is less with metronidazole than with benzyl penicillin.⁶ This is because benzyl penicillin is a GABA antagonist, which may decrease the spasm threshold. Alternative antibiotics include doxycycline and carbapenems. Activity against the organism is also demonstrated by macrolides and cephalosporins.

Tetanus immune globulin should be given in the first instance to remove unbound tetanus toxin. It does not affect toxin bound to nerve endings. Tetanus disease does not result in tetanus immunity because of the extreme potency of the toxin, and active immunization with tetanus toxoid should begin when the patient's condition improves, before discharge from hospital.

Sympathetic over activity is a major cause of tetanus-related death in the intensive care unit and is usually treated with labetalol. Beta blockade alone may result in unopposed alpha-adrenergic activity resulting in severe hypertension. Other complications that commonly arise include nosocomial infections and pulmonary embolism.

Discussion

The cases described above bear similarities in presentation and management. All presented with difficulty in using the oropharyngeal musculature. Indeed 50-75% of patients with tetanus present with trismus. It seems the tendency is for them to be referred to the ENT department for assessment, and the likelihood is that they will be diagnosed here. Alternatively they

Table 1: Guidelines on Tetanus wound management⁶

Immunisation History	Clean, non-tetanus prone wounds		Dirty, tetanus prone wounds	
	ATT	ATIG	ATT	ATIG
Unknown or < 3 doses ever	Yes	No	Yes	Yes
3 or more doses ever	No*	No	No**	No

* Yes if >10 years since last dose; ** Yes if > 5 years since last dose

may present to the dental surgeons. It is therefore important for practitioners in both these specialities to retain a high index of suspicion for this disease.

Although there is a definite differential diagnosis, the most similar presentation being strychnine poisoning, physicians with experience in this illness should not find major difficulty in arriving at a diagnosis and initiating treatment. Strychnine levels should be taken, but institution of treatment cannot wait for the results of this test. In cases of doubt, referral to the Infectious Disease team should be done.

The spatula test was used in Case 4, but was negative, ie. the patient rejected the spatula when this was introduced into the mouth. This is a normal reflex. In tetanus, the test turns positive, and the patient bites on the spatula because of reflex spasm of the masseters. This test was 94% sensitive and 100% specific in a study involving 400 patients.⁷

All four were treated with dual antibiotic treatment initially. Metronidazole was found to be better tolerated than benzyl penicillin in one clinical study. However the benefit of administering both antibiotics together is not known. A literature search did not reveal any studies looking for survival advantage with this regimen. All four patients survived but the benefit, if any, that dual antibiotic treatment had on the outcome cannot be determined. Studies have shown an association of increased mortality with increasing age. In our case, all four patients were above 60 years of age. The mortality in unvaccinated individuals in the United States is 15%.

All patients spent between 30-40 days on intensive care. They were all treated with a magnesium sulphate infusion in line with current trends. In our context, it was not used as a substitute to ventilation, but as an antispasmodic in conjunction with ventilation. However, in Case 4, ventilation was avoided

altogether, probably with the help of magnesium sulphate. Our experience showed that it is well tolerated and a useful adjunct to benzodiazepines.

The incidence of tetanus in Malta has decreased since the late 1970's. This is probably due to better uptake of immunisation since this was made mandatory. Also, increased awareness of the disease could have led to better tetanus prophylaxis administered at the primary level for at risk injuries. A similar decline has been observed in other countries such as the United States where the number of cases has fallen from 0.5/100,000 in 1947 to 0.02/100,000 in 1990.⁸ The rise in cases in Malta during 2003 cannot currently be explained.

Clearly the key to overcome this disease lies in prophylaxis. Tetanus is a preventable disease and there should be no excuse as to why people are not immunised against it. Moreover, when wounds at risk occur, they should be thoroughly cleaned and dead or devitalized tissue removed. Further management of the patient is outlined in the Guidelines seen in Table 1, depending on the type of wound sustained (Table 2). Administration of prophylactic antibiotics should be considered if the immunisation history is unknown or if less than 3 doses of ATT have been given ever. However, the importance of proper immunisation of patients with wounds at risk cannot be overemphasised.

Conclusion

Tetanus is an illness that has been largely overcome in Malta, but a very low level of incidence is still present. This is probably due to an effective immunisation programme, as well as proper management of tetanus prone wounds. The potential benefit of dual antibiotic treatment with benzyl penicillin and metronidazole may warrant further study.

Table 2: Wound classification⁹

Clinical Features	Tetanus prone	Non-tetanus prone
Age of wound	>6 hours	<6 hours
Depth	Stellate, >1cm	<1cm
Mechanism of injury	Missile, crush, burn, frostbite	Sharp surface (glass, knife)
Contamination	Present	Absent
Devitalised tissue	Present	Absent

References

1. World Health Organization. Vaccine-preventable diseases: monitoring system. Geneva: WHO, 2001:18-19. (WHO/V&B/01.34).
2. Thwaites C L, Farrar J J. Preventing and treating tetanus. *Br Med J* 326:117-118, 2003
3. Goulon M, Girard O, Grosbius S et al. Les corps antitetaniques. *Nouv Presse Med.* 1972;1:3049-50.
4. Attygalle D, Rodrigo N. Magnesium as first line therapy in the management of tetanus: a prospective study of 40 patients. *Anaesthesia.* 2002 Aug;57(8):811-7.
5. Bhatia R, Prabhakar S, Grover V K. Tetanus. *Neurol India.* 2002 Dec;50(4):398-407.
6. Ahmadisyah I, Salim A. Treatment of Tetanus: an open study to compare the efficacy of procaine penicillin and metronidazole. *Br Med J* 291:648, 1985.
7. Apte NM, Karnad DR Short report: the spatula test: a simple bedside test to diagnose tetanus. *Am J Trop Med Hyg* 1995 Oct; 53(4): 386-7.

8. Sutter RW et al. Tetanus. In: Hoeprich PD, Jordan MC, eds. *Infectious Diseases: A Modern Treatise of Infectious Processes.* 5th ed. Philadelphia: JB Lippincott, 1994.
9. Adapted from *MMWR* 39:37,1990; *MMWR* 46 (SS-2):15, 1997
10. *ACS bulletin* 69:22.23 1984 No 10

Bibliography

Mandell GL, Bennett JE, Dolin R: *Principles and Practice of Infectious Diseases*
The Sanford Guide to Antimicrobial Therapy 2003. Thirty-third edition

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