Elevated Antitoxin Titers in a Man with Generalized Tetanus

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Vaccination programs have significantly reduced the incidence of tetanus in the United States. The disease develops almost exclusively in those who have been inadequately immunized. This report describes severe, generalized tetanus in a 29-year-old man who had received a primary series as a child and two booster injections. Serum obtained before administration of tetanus immune globulin showed antibody titers to tetanus greater than 100 times the level considered protective. Aggressive supportive care can usually prevent serious consequences. Since most physicians have never seen a case of tetanus, however, the diagnosis can be difficult. Many disorders that exhibit signs and symptoms similar to tetanus must be carefully considered during the evaluation of these patients.

Tetanus is a preventable disease. Prevention, however, requires both appropriate immunizations and prompt wound care. While controversy exists regarding the most effective policy to adequately immunize all individuals, this case shows that vaccination alone does not preclude the possibility of tetanus.

KEY WORDS. Tetanus; tetanus antitoxin; immunization; tetanus toxoid *(J Fam Pract 1997; 44:299-303)*

Fewer than 100 cases of tetanus are reported in the United States each year, primarily because of immunization programs that began in the 1940s.[1] The disease occurs almost exclusively in those who are inadequately immunized. A recent serologic survey demonstrated that significantly lower rates of immunity, and therefore greater risk of infection, exist in the elderly, in Mexican Americans, in those living in poverty, and in those with lower levels of education.[2] Even among older school-aged children (aged 10 to 16 years), 20% are not immune to tetanus.[2] It has been assumed that, in those who have been vaccinated, tetanus either does not occur or follows a much milder course. Isolated case reports document the rare occurrence of tetanus in persons with protective antibody levels.[3-6]

We present a case of a 29-year-old man who developed severe, generalized tetanus, despite having received a primary series and two booster injections. Because the disease portends significant morbidity and mortality, it must be rapidly recognized and differentiated from illnesses with a similar presentation, such as hypocalcemic tetany, meningitis, rabies, drug withdrawal, strychnine poisoning, and dystonic drug reaction. Once identified, tetanus demands aggressive treatment. Since most physicians have never seen a case of tetanus, the diagnosis can be difficult. With little help from laboratory tests, the correct diagnosis depends on the recognition of classic clinical features and the exclusion of alternative diagnoses.

Submitted, revised, August 5, 1996.
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Case Report

A 29-year-old man with a history of amphetamine abuse was brought to the emergency department by his wife and employer because of severe agitation and muscle spasms. During the workup for admission to the drug rehabilitation unit, the emergency physician noted a temperature of 101.2°F, a white blood cell count of 11,600 mm^3, and diffuse muscle spasms with agitation. These findings were initially attributed to drug withdrawal, and the patient was given intravenous lorazepam.

Subsequent questioning of the patient revealed that 8 days before, he had punctured his right foot on a rusty nail as he walked barefoot along a riverbank. Four days after the injury, he experienced cramping in his calves, and on the 5th day he became restless and agitated and exhibited "jerky" movements. On day 6 he had difficulty swallowing and developed painful orofacial spasms. By the following day, the day of admission, his leg spasms had become so

severe that he was unable to walk. He had not slept for several days, despite self-medicating with diazepam and diphenhydramine. The remainder of the history was significant for his immunization record, documenting that he had had a primary DPT series and booster injections at ages 12 and 23.

On initial examination, the patient was alert and oriented. A normal blood pressure and pulse were noted. He exhibited repetitive spasms of the facial muscles that produced a fixed grinning expression and elevated eyebrows (risus sardonicus). The patient demonstrated crossed patellar reflexes and developed multiple, painful, generalized spasms and opisthotonos with even the slightest tactile stimulation. He was not drooling, but refused to swallow, and could not open his jaw. His abdomen was rigid with tonic contractions of the rectus muscles but he did not exhibit other findings of peritonitis on examination. A tender, mildly erythematous puncture wound, without purulent drainage, was noted on the lateral plantar surface of the right foot. The neurologic examination demonstrated hyperactive deep tendon reflexes with clonus, spontaneous Babinski reflex, and spasmodic extension of the lower extremities. No mydriasis or piloerection was detected. The remainder of the examination was unremarkable.

Pertinent laboratory tests revealed white blood cell count (WBC) of 11,600 mm^3 with 74% neutrophils, but no left shift, and BUN, creatinine, and electrolytes all within normal limits, CPK 3621 µ/L, calcium 9.4 mg/dL, albumin 4.2 g/dL, and CO_2 25 mEq/L. Urinalysis showed trace ketones and specific gravity 1.034. Wound cultures were subsequently negative for *Clostridium tetani*. Drug screening tests were positive for phenylpropanolamine, diphenhydramine, and benzodiazepine and negative for strychnine, phenothiazines, haloperidol, and tricyclics. As determined by the mouse neutralization assay, tetanus antitoxin levels in the initial serum samples showed titers between 1.0 and 10 IU/mL.[7]

The patient was given tetanus immune globulin and admitted to the intensive care unit in a quiet, dark room. Intravenous phenobarbital (>600 mg/day) and diazepam (>100 mg/day) failed to control the spasms. Consequently, a continuous pentobarbital infusion was used to keep the patient deeply sedated, and an elective tracheostomy was performed to protect the airway. The foot wound was debrided and anaerobic cultures were obtained both in the emergency department and at the time of the tracheostomy. Penicillin G was given to treat the infection. Hydration and nutrition were maintained through a feeding tube. Frequent turning was needed to prevent decubitus ulcers, and padding was used to protect the patient from injury during the spastic episodes.

After 3 days the pentobarbital infusion was temporarily stopped to check the patient's condition. Unfortunately the patient continued to demonstrate opisthotonic posturing, trismus, and spasticity, so the pentobarbital drip was restarted. The infusion was continued until the 11th hospital day. At that time, although the patient demonstrated hyperreflexic deep tendon reflexes, the patellar reflexes no longer crossed, cortical function was intact, and the patient was able to open his mouth and swallow. He was extubated shortly thereafter and discharged several days later. The hyperreflexia persisted for months.

Discussion

Tetanus is a rare disease in the United States with only 50 to 60 cases reported each year.[8] It is caused by *Clostridium tetani*, a spore-producing, anaerobic, gram-positive bacillus. When these spores are exposed to an anaerobic environment in a contaminated wound, they germinate and begin to produce exotoxins. While two toxins, tetanospasmin and tetanolysin, are produced, tetanospasmin is responsible for manifestations of the disease. Tetanospasmin enters alpha motor neurons through the motor endplate both at the site of infection and elsewhere as it is carried through the bloodstream. Once the toxin enters the alpha motor neurons, it is protected from attack by antibodies.[9] Consequently, symptoms may continue to progress for 10 to 14 days after treatment with antitoxin. Inside the alpha motor neurons, toxin travels by reverse axonal transport to the cell body in the anterior horn of the spinal cord. Tetanospasmin diffuses out into the central nervous system, where it enters other neurons and blocks release of neurotransmitters, perhaps permanently. GABAergic and glycinergic inhibitory neurons are particularly affected. The loss of inhibitory input allows small excitatory potentials elicited by minimal stimulation to cause indiscriminate firing of motor neurons. This results in the diffuse muscle spasms seen in clinical tetanus.

The diagnosis of tetanus can present problems for

physicians, most of whom have never seen a case of tetanus. Laboratory tests provide indirect evidence of the disease, but no specific tests are rapidly available. Wound cultures can be helpful if they are positive, but a negative culture is of little value. In confirmed cases of tetanus only 30% of wound cultures isolate the organism.[10] Ultimately, the physician must rely on pertinent historical and physical examination findings. Common findings include trismus (lockjaw), risus sardonicus, opisthotonic posturing, and autonomic dysfunction. Despite its activity in the central nervous system, tetanus does not alter the sensorium. The disease must be differentiated from conditions with similar presentations, such as hypocalcemic tetany, meningitis, rabies, drug withdrawal, strychnine poisoning, and a dystonic drug reaction.[11-13]

A combination of key clinical features and a few simple laboratory tests will usually distinguish tetanus from its counterfeits. A normal serum calcium excludes hypocalcemic tetany. Patients with meningitis usually exhibit some degree of central nervous system depression and nuchal rigidity, but no generalized muscle spasm. Although rabies can appear similar to tetanus, patients with rabies foam at the mouth, reject water, develop dementia and, as a rule, do not recover.

The patient's history of drug use prompted careful consideration of drug withdrawal in the differential. Several key findings, however, make drug withdrawal an unlikely diagnosis. Withdrawal can cause a sort of "sympathetic overdrive" manifested by spasticity, mydriasis, piloerection, and impaired consciousness.[12] This patient had spastic contractions but demonstrated a normal sensorium and no mydriasis or piloerection. In addition, the symptoms remained for weeks and did not respond to massive doses of diazepam (>100 mg/day).

Strychnine, commonly used in street drugs as a "cutting" agent, produces clinical findings almost indistinguishable from tetanus. Symptoms from poisoning, however, usually resolve over several days, and the drug can be detected in the urine.

Dystonic drug reactions manifest as muscle spasms associated with ingestion of haloperidol, piperazines, or tricyclic antidepressants. Although the spasms of dystonic reactions are usually limited to the face, cases of generalized spasms have been described.[11] Dystonic drug reactions, however, like other extrapyramidal symptoms, respond quickly to diphenhydramine, and the associated drugs are easily identified in the urine.

After considering the many alternatives, tetanus appeared to us to be the most likely cause. The prolonged course of repetitive, painful, generalized spasms, and the failure to detect potential causative agents strongly suggested the diagnosis. The occurrence of a contaminated wound only a few days prior to the onset of symptoms provided additional confirmation. Some findings, however, seemed inconsistent with tetanus. While this patient's fever was consistent with the autonomic dysfunction seen in tetanus, his pulse and blood pressure were initially normal. The autonomic dysfunction of tetanus can be either sympathetic or parasympathetic, or may be absent, but is more often a sort of hypersympathetic state. The hypersympathetic state is similar to that seen in alcohol withdrawal and is effectively treated with benzodiazepines. This patient's self-prescribed treatment with diazepam may have masked any underlying autonomic dysfunction.

To prevent the serious consequences of tetanus, physicians must quickly identify the disorder and administer aggressive supportive care, including tetanus immune globulin, antibiotics, and medication to control the spasms. In this case the patient's infection was treated with intravenous penicillin G, although a recent nonrandomized study[14] suggests that metronidazole may be preferable to penicillin. The pentobarbital drip allowed minute-to-minute control of the patient's level of sedation and provided safe, effective relief from the spasms.

Over 90% of the cases of tetanus occur in those who did not receive a primary immunization series.[1] Serologic studies document high tetanus antibody levels 20 years after an individual receives a primary series and one booster.[15] Antibody levels greater than 0.01 IU/mL, as determined by the mouse neutralization assay,[16,17] are considered protective. Our patient's antibody levels at presentation, before immune globulin was administered, were between 1.0 and 10 IU/mL, over 100 times the protective level. Occasionally, mild tetanus occurs in those with high antibody levels.[3-5] Severe tetanus, however, has been reported in only three patients with protective levels.[6] Nonetheless, the idea of a universally protective level has been questioned. Even Sneath, whose original work helped to establish the standard for the protective level, noted that 13% of the guinea pigs developed clinical tetanus despite antibody levels as

high as 0.1 to 0.5 IU/mL.[16]

Much conjecture, but very little evidence, exists to explain how tetanus occurs in persons with high antibody levels. Crone and Reder[6] suggest that the appearance of tetanus in those with high antibody levels may be due to antigenic variability between toxin and toxoid. Our patient's titers, however, were measured using the mouse neutralization assay.[7] In this assay the patient's serum is added to native toxin and the mixture is injected into mice. Only antibodies with direct biologic activity able to block manifestations of tetanus in the mice are measured. Perhaps this patient's deep, necrotic wound allowed large amounts of toxin to access alpha motor neurons directly at the site of the injury, thereby bypassing immune surveillance.

The high antitoxin titers detected in our patient at the time of presentation may not reflect the antitoxin levels that were present at the time of the initial infection 8 days earlier. Wohlters and Dehmel[18] demonstrated that native toxin can elicit large increases in antitoxin titers when the exposure to native toxin occurs in a previously immunized individual. If this were the case in our patient, high titers of antitoxin would represent an immune response to the toxin released at the wound site. His development of disease may reflect a combination of low antitoxin titer at the time of infection and the bypassing of immune surveillance through direct access to alpha motor neurons at the site of infection.

For now, the most important preventive measure is to administer a primary series and periodic boosters. Although the Advisory Committee on Immunization Practices (ACIP) continues to recommend booster injections every 10 years,[19] others advocate a modified strategy based on the long duration of high antibody levels following the primary series.[20] The US Preventive Services Task Force recommends the initial five-dose series in childhood followed by Td boosters every 15 to 30 years for those living in the United States. Boosters should be given every 10 years to international travelers.[21] Also, ACIP guidelines must be applied to the care of contaminated wounds. In one study, 23% of patients who presented to emergency departments with tetanus-prone wounds were treated inappropriately.[22]

To protect our population from the severe consequences of this preventable disease, we must not only continue to press for increased rates of vaccination in preschool children, we must also direct our resources to others who are inadequately immunized. Since most of the cases and almost all of the fatalities occur in those over the age of 60,[1] this group deserves our principal efforts. The American College of Physicians Task Force on Adult Immunizations and the Infectious Diseases Society of America recommend linking assessment of vaccination status and administering vaccines at age 50 to other well-established preventive health measures.[23] In a similar recommendation, the ACIP advises that for patients 50 years old, besides offering other preventive services, physicians should (1) review their immunization status, and (2) administer tetanus and diphtheria toxoids as indicated.[24] Sanford has stated, "A case of tetanus reflects the failure of our health care delivery system to provide immunization."[25] Except for rare, isolated cases, the assertion is profoundly accurate.

ACKNOWLEDGMENT

We thank Dr Jane Halpern at the National Institutes of Health for graciously conducting the mouse neutralization assays on our patient's sera.

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