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Pediatrics 2007;120;e1355
DOI: 10.1542/peds.2006-3386

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Atypical Tetanus in a Completely Immunized 14-Year-Old Boy

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

We report the uncommon clinical course of tetanus in a completely immunized 14-year-old boy. His initial symptoms, which included a flaccid paralysis, supported a diagnosis of botulism. Preliminary mouse-test results with combined botulinum antitoxins A, B, and E, obtained from tetanus-immunized horses, backed this diagnosis. The change in his clinical course from paralysis to rigor and the negative, more specific, botulinum mouse test with isolated botulinum antitoxins A, B, and E, obtained from nonvaccinated rabbits, disproved the diagnosis of botulism. Tetanus was suspected despite complete vaccination. The final results of a positive mouse test performed with isolated tetanus antitoxin confirmed the diagnosis. Adequate treatment was begun, and the boy recovered completely.

Today, tetanus is a rare disease in countries with primary immunization programs. The reported incidence for adults and children is low, with an average of 43 cases per year in the United States, 1 12 to 15 per year in the United Kingdom, 2 and <15 per year in Germany. 3 However, tetanus occurs occasionally despite complete vaccination status. In these cases, the clinical picture can be altered, which hampers accurate and timely diagnosis. Here we report the unusual clinical presentation of tetanus in a completely immunized 14-year-old German boy.

CASE REPORT

The patient was admitted to our hospital with a 1-day history of headache, left-sided ptosis, generalized paresthesia, and impaired vision. His oral mucous membranes were extremely dry. Three days before he had suffered from mild diarrhea, and the day before admission he had eaten grilled chicken with barbeque sauce. The parents recalled a tick bite 1 year ago and an accidental abrasion at the patient’s left knee 1 week before, when the boy scratched himself on the rough surface of wooden floorboards. He did not clean the wound, and at admission it was small (2–3 mm in diameter), dry, and in the process of healing. In his spare time, the patient, who is right-handed, used to work with lacquers and glue. His medical history was uneventful. He had had chicken pox at the age of 3 years and common upper respiratory tract infections in his infancy. His immunization schedule was up-to-date with initially 3 vaccinations in the first year of life and a tetanus booster 1 year before presentation. Communication with the patient’s doctor and with the manufacturer of the vaccine revealed that the booster was within the vaccine’s expiration date and that there were no reports of reduced quality of that production lot.

After admission, an antibiotic and antiviral treatment with ceftriaxone (200 mg/kg per day), clarithromycin (15 mg/kg per day), and acyclovir (30 mg/kg per day) was initiated for suspected early meningoencephalitis despite normal cerebrospinal fluid test results. The results of microbiologic and virologic examinations (cultures and polymerase chain reaction for bacteria and fungi, ameba, toxoplasmosis, Mycoplasma, Borrelia, Chlamydia, rabies, herpes simplex 1–2, HIV 1/2, cytomegalovirus, Epstein-Barr virus, enterovirus, early-summer meningococcal, measles, varicella, influenza and parainfluenza 1–3, and parvovirus B19) in blood and cerebrospinal fluid were negative. Results of drug

Key Words: tetanus, botulism, infection, immunization, paralysis, mouse toxicity test

Abbreviation: IgG, immunoglobulin G

Accepted for publication Apr 17, 2007
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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2007 by the American Academy of Pediatrics

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screening, an edrophonium-provocation test, and testing of autoimmune antibodies (antineutrophil cytoplasmic antibody, antinuclear antibody, antimitochondrial antibody, and antibodies against neurons, myelin, glycoprotein, and ganglioside) were negative.

On day 2, the patient’s condition deteriorated severely, with alternating hypopnea and tachypnea, anxiety, hyporeflexia, bilateral ptosis, oculomotor nerve palsy, photophobia, dysarthria, dysphagia, and flaccid paralysis of the trunk and lower limbs. The patient was transferred to the PICU. Repeated electroencephalography, neurophysiologic examinations, and cerebral MRI and magnetic resonance angiography were normal. Treatment with intravenous immunoglobulin (Gamunex 10% [Bayer Healthcare AG, Leverkusen, Germany], 2 g/kg = 100 g over 5 days intravenously) was started for suspected Guillain-Barré syndrome. Because an atypical botulism infection could not be completely excluded, equine botulinum antitoxin (Botulismus-Antitoxin [Chiron-Behring GmbH & Co KG, Marburg, Germany], 1 mL = 750 IU of botulinum antitoxin A, 500 IU of antitoxin B, and 50 IU of antitoxin E) was added on day 3. The antidote treatment was ceased at 350 of 500 mL because of an anaphylactic reaction. On the same evening he developed urine bladder dysfunction, carpopedal spasms, intermittent rigors of the upper limbs, and increasing rigors of the lower limbs and hypopnea. He received midazolam (0.04 mg/kg per hour intravenously), tetracetam (1 mg/kg per day orally), and metamizole (80 mg/kg per day intravenously) to control spasms and pain. Hypopnea and apnea were treated with theophylline (initially 5 mg/kg, then 4 × 2.5 mg/kg per day intravenously) and oxygen supplementation.

The next morning our patient showed risus sardonicus and permanent rigor of the upper and lower limbs. These symptoms supported a clinical diagnosis of tetanus. Therefore, he was treated with 10 000 IU of tetanus antitoxin. Antibiotic treatment was changed to metronidazole (20 mg/kg per day). The retrospective tetanus-immunoglobulin G (IgG) level at admission was 2.11 IU/mL.

Twenty-four hours after initiation of the tetanus treatment, his neurologic status remained stable. On day 5 he developed transient bradycardia with prolonged QTc time interval (QT/QTc: 490/476 milliseconds). After 8 days his painful spasms became more infrequent. One day later, he responded to questions by nodding. On day 15, the dysarthria improved, and his speech became partially understandable; on day 17, he showed normal or slightly decreased muscular reflexes and increased muscular tone of all 4 limbs. He was able to sit upright unsupported, and his muscular strength of the upper limbs was 3/5 to 4/5. His right-sided ptosis resolved and improved on the left side. After 3½ weeks the patient was transferred to a rehabilitation center.

Fourteen days after discharge he was able to walk independently with normal power of the upper limbs and lower-limb power at 4/5. His muscular reflexes and fine motor skills were slightly reduced. Minimal ptosis on his left side persisted. At follow-up 6 months and 1 year later his neurologic and psychological examinations were completely normal.

**DISCUSSION**

Tetanus occurs in different clinical patterns, with generalized tetanus as the most common form. It is caused by the Gram-positive, spore-forming *Clostridium tetani*, which produces its toxins (tetanospasmin and tetanoly- sin) in a favorable environment, preferentially in tissue wounds. Tetanospasmin is able to block neurotransmitter release, which leads to the characteristic increased muscle tone and spasms. In the typical course of tetanus, patients often first notice trismus. Subsequently, dysphagia and stiffness or pain in the upper trunk muscles appears, followed by descending muscular rigidity. Other common clinical manifestations are risus sardonicus, the continuing contractions of face muscles, and an opisthotonos. The clinical course can be complicated by apnea, laryngospasm, aspiration pneumonia, and autonomic dysfunction with need for intensive care management.

In our patient, initial paralysis and dry mouth, after consumption of grilled meat, misled to a diagnosis of botulism and seemed to be confirmed by the positive mouse toxicity test for botulism: the mice died after injection of the patient’s blood serum but survived after administration of the patient’s serum mixed with botulinum antitoxins A, B, and E (Fig 1). However, as the clinical signs changed from flaccid paralysis to the tetanus-typical rigor, tetanus became clinically obvious despite the patient’s history of appropriate tetanus vaccination. At this stage, the in vivo mouse test had to be doubted. Mice treated with blood serum and botulinum antitoxin, containing antibodies specific for type A, B, or E botulinum toxin separately, became severely paralyzed or died, as did the control mice that received the patient’s blood serum only. The assumed explanation seemed unconventional but simple: single antitoxins originate from rabbits, whereas the combination of A, B, and E botulinum antitoxins is obtained from horses. In contrast to rabbits, horses are routinely immunized against tetanus. Thus, the combined botulinum antitoxin mixture also contained tetanus antitoxin. Conclusive results were obtained by the tetanus mouse test (adapted from the work of Habermann and Wiegand4). Mice that received the patient’s blood serum plus tetanus antitoxin survived without symptoms. This result led to the eventual diagnosis of atypical tetanus in a fully vaccinated child.

On the basis of its exquisite sensitivity, the gold standard of botulinum and tetanus neurotoxin detection is still the mouse toxicity test5,6: the lethal amount for
botulinum toxin is in the range of 0.5 to 1.2 ng per kg of body weight (depending on the botulinum toxin subtype, intraperitoneal injection route), and for tetanus toxin it is 1 ng per kg of body weight (intraperitoneal injection route). Taking into account the maximal injection volume of 1 mL and an average mouse weight of 20 g, this results in a sensitivity of 10 to 20 pg/mL.

The procedures for the mouse toxicity test for botulinum and tetanus toxin are similar:

- The patient material is injected intraperitoneally into mice, and symptoms are observed for several hours up to 4 days. In the case of botulinum toxin intoxication, mice sequentially show ruffled fur, labored but not rapid breathing, a characteristic wasp-like abdomen with narrowed waist caused by increased respiratory effort, weakness of limbs that progresses to total paralysis, and gasping for breath followed by death as a result of respiratory failure. In the case of tetanus toxin intoxication, similar symptoms may occur. However, the characteristic wasp-like abdomen with its narrowed waist is only described in mice after administration of botulinum toxin. This symptom is usually missing when testing for tetanus toxin, and spastic paralysis indicates the presence of tetanus toxin.

- Death of mice in the absence of neurologic symptoms is not an acceptable indication of botulism or tetanus, because it may be nonspecifically caused by other microorganisms, chemicals present in the test fluids, or injection trauma.

- Confirmation and exact neurotoxin typing is performed by mouse-protection tests using polyvalent or monovalent neutralizing antibodies (which is better) as in our studies and the respective neutralizing antibodies, the mice are rescued and no symptoms occur.

Currently, the mouse-protection test is still the standard method of choice for quantifying tetanus toxin-neutralizing antitoxin titers. Furthermore, the mouse assay for botulinum toxin is used most frequently for detecting botulinum toxin in foods or patient material or for assessing the potency of the toxin used as a drug in medicine.

In our case, other differential diagnoses such as myasthenia gravis, Guillain-Barré syndrome including variants, encephalitis, lupus erythematosus or other autoimmune reactions, tumor, leukemia, botulism, and intoxication seemed very unlikely, because the results of repeated MRI and laboratory results were completely normal, and the patient’s clinical signs changed quickly from paralysis to rigor. A rare differential diagnosis of tetanus is strychnine poisoning with some similar symptoms such as restlessness, anxiety, muscle twitching, intense pain, trismus, facial grimacing, opisthotonus, and extensor spasm. The rapid onset of symptoms in strychnine poisoning, usually 10 to 20 minutes, made this diagnosis unlikely for our patient, because his clinical picture first showed flaccid paralysis, and rigor of the limbs and risus sardonicus occurred the next day. Hence, a screening for strychnine and alkaloids of Strychnos species was not performed. The intermittently observed bradycardia with prolonged QT-time interval has been described in patients with tetanus.

An increased incidence of tetanus in countries with immunization programs has been reported in elderly adults with impaired immunity despite preceding vaccination. In children with adequate immunization, there have been only a few case reports of tetanus infections. Our patient’s tetanus-IgG level at admission was 2.11 IU/mL, which is considered to be long-lasting protection against infection (range: 1.1 to 3 IU/mL). This level was rechecked at the same laboratory. Unfortunately, no serum was left from the initial blood sample.
for retesting in another institution; the patient had already been treated with immunoglobulin and botulinum antitoxin before the eventual diagnosis of tetanus was made. However, it should be noted that the indicated antitetanus IgG level summarizes protecting and non-protecting antibodies. If the patient has either a low quantity of protecting antibodies in the serum or, alternatively, the concentration of the toxin is too high to be neutralized by the circulating protecting antibodies, the patient develops tetanus and the mouse test for tetanus gives a positive result. Crone and Reder speculated in their case series that burden of toxin can overwhelm patients’ defenses or that an antigenic variability between toxin and toxoid could cause immunization failure.

Treatment of tetanus is based on 3 principles: neutralization of unbound toxin, prevention of additional toxin release, and amelioration of ongoing symptoms. Early, aggressive, intensive care treatment is indicated to prevent or alleviate fatal complications such as respiratory failure and autonomic dysfunction.

Although unintended, but presumably life saving, our patient was treated early for tetanus: he received at least 750 IU of tetanus antitoxin with the botulinum antitoxin (Chiron-Behring GmbH & Co KG, verbal communication, 2005) and an additional 2000 IU with the immunoglobulin infusion (Gamunex 10% has an average content of tetanus antitoxin of 2 IU/mL [Bayer Healthcare AG, verbal communication, 2005]).

CONCLUSIONS

Atypical tetanus should be considered as a rare differential diagnosis in patients with neurologic symptoms despite complete tetanus vaccination. It can be proven unequivocally by the mouse toxicity test.

REFERENCES

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