Peripheral Neuropathy Following Tetanus Toxoid Administration

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The incidence of anaphylaxis to horse serum administration is estimated to be one in 50,000 and that of serum sickness one in 20. This significant risk has served to emphasize the superiority of active immunization against tetanus with toxoid over passive immunization with heterologous antitoxin. Significant local and systemic reactions to tetanus toxoid were not uncommon with the cruder preparations of yesteryear but have become less frequent with those currently available.

In 1940, Cooke1 reported cases of urticaria following booster injections of tetanus toxoid. This was shown to be due to the Berna peptone used in the culture media. A review of reactions to tetanus toxoid by Whittingham in 19402 indicated that acute anaphylactic reactions occurred in two of 61,000 inoculations or 0.003%. The incidence of constitutional and significant local reactions in the same series was 1%. The sensitizing agent in most of these cases was considered to be the Witte peptone used in the broth. Several additional reactions were attributed to the silk used in the filtering process.3 A few reactions, of the delayed type, were shown to be due to the toxoid itself.4

With improvement in the technique of preparation, the rate of significant tetanus toxoid reactions in large military immunization programs is now reported at only 0.002%.5 Reports from civilian centers,6 however, give the impression that the delayed reactions consisting of local swelling, erythema, lymphadenopathy and fever occur considerably more frequently than these figures indicate. These reactions have been observed more frequently with the alum preparations than with the fluid toxoid.6 Positive immediate wheal and flare reactions to the commercially available undiluted tetanus toxoid are not uncommon in persons demonstrating hypersensitive reactions. Few of them, however, are capable of being passively transferred.7

The case to be presented is noteworthy because it cites the occurrence of a peripheral neuropathy following tetanus toxoid administration, and to our knowledge, a reaction never recorded heretofore.

Report of a Case

A 23-year-old white male medical student was admitted to Temple University Medical Center on March 17, 1963, with a history of having injured himself the previous afternoon while playing tennis and sustaining an abrasion of the right knee. The previous evening, he had received an injection of 0.5 cc fluid tetanus toxoid in the right deltoid muscle. At 1 AM on the day of admission, seven hours after the injection, he awoke to find that wrist drop of the right hand had developed. By morning there was complete motor and sensory paralysis over the distribution of the right radial nerve.

The history was otherwise noncontributory except for a personal history of asthma during childhood and the appearance of hay fever at age 20.

Physical examination on admission, 24 hours after the injection, revealed a temperature of 100.6 F (38.1 C) orally. There was a right wrist drop with loss of sensory function over the area mediated by the radial nerve. A mild erythematous rash was present over the upper right arm and the right anterior aspect of the chest.

Routine admission blood and urine studies were unremarkable.

The therapy consisted of diphenhydramine hydrochloride 50 mg by mouth, four times a day. By evening on the day of admission the entire arm and hand were swollen and edematous with induration localized to the site of the injection. A few petechiae were present on the dorsum of the hand. The fever and edema subsided within 24 hours. About this time there was evidence of partial return of radial nerve motor function. The patient was discharged on March 19, 1963. Follow-up showed that sensory function improved gradually. No residual motor or sensory deficit could be detected one month later.

Three months after admission direct skin tests by the intracutaneous method showed moderate wheal and erythema reactions to the 1:10 dilution of fluid toxoid. Passive transfer with the patient's serum was also positive indicating the presence of a significant titer of skin-sensitizing antibody.

Two years later direct skin tests by the intracutaneous method were still positive to several commercial toxoid preparations and to a nonirritating dilution of the crude unrefined toxoid. A negative skin reaction was obtained with the culture media used in the production of toxoid. This eliminated the media as the agent responsible for the positive skin reaction and tended to corroborate the specificity of the reaction to the toxoid per se. Passive transfer with the patient's serum at this point failed to give positive reactions, indicating that the titer of skin-sensitizing antibody was now below the threshold required for a positive Prausnitz-Küstner reaction.

Comment

In 1952, Kuhns and Pappenheimer4 noted that allergic persons developed a skin-sensitizing, nonprecipitating antitoxin to immunizing injections of diptheria toxoid. This nonprecipitating antitoxin exhibited most of the properties of atopic reagin; that is, it could be passively transferred and remained fixed to normal skin for periods up to four weeks, it did not fix complement, and its skin-sensitizing ability was destroyed by heat. The direct wheal and flare reaction seemed to parallel the antitoxin titer and became subthreshold in a few weeks. They believed that atopic persons possessed an altered immunologic mechanism responsible for the production of reaginic rather than classical precipitating antitoxin.

On further study, using tetanus toxoid as the

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immunizing agent, Kuhns11 demonstrated that nonallergic persons could also develop immediate skin reactivity of the type previously described, although it required more injections and a larger total antigenic dose. Furthermore, the response was less persistent than in atopic persons.

These findings are similar to those of Feinberg et al,19 who obtained similar results with a different antigen (pollen) in a water and oil emulsion vehicle. They noted that, in response to such injections, atopic persons developed immediate-type hypersensitivity with skin-sensitizing antibody, indistinguishable from reagin, while the nonatopic group usually developed delayed reaction hypersensitivity. Atopic persons developed wheal and flare reactions more consistently, in a shorter period of time and of greater persistence than did the normal, nonallergic controls. The latter, however, could be made to develop skin-sensitizing antibodies with repeated antigenic stimulation. None of the volunteer subjects developed clinical allergy to the injected antigens.

Our finding of the development of immediate type hypersensitivity with its accompanying skin-sensitizing antibody following tetanus toxoid administration in an atopic person parallels Kuhns and Pappenheimer's original observation. However the persistence of a positive wheal and flare intracutaneous test to tetanus toxoid two years after the reaction and its failure to then be passively transferred deserves further comment. One such explanation might be that the agent responsible for the original skin test and positive passive transfer consisted of two components; the first an atopic reagin to tetanus toxoid that persisted to date; the second, a more labile type of skin sensitizing antitoxin similar to those demonstrated by Kuhns that decreased significantly in the interval between the Prausnitz-Küstner tests. The latter would explain the heightened reaginic titer responsible for the positive passive transfer three months after the reaction and its absence two years later.

It might also be explained by the persistence of a low level of circulating nonprecipitating antitoxin from the original antigenic stimulation two years before. The clinical picture plus the immunologic findings suggest an accelerated serum-sickness type syndrome mediated by toxic-complex formation as the mechanism responsible for the observed reaction.

The present case is unique because of the development of radial nerve paralysis. Peripheral nerve paralysis following horse tetanus antitoxin administration is well recognized as an integral part of the serum-sickness syndrome.13 This has frequently been referred to as serum neuritis and has been reported as the only manifestation of serum sickness.4 The nerve damage in these cases may at times be irreversible. Formation of microprecipitates of antigen-antibody complexes in vessels nourishing nerves or the occurrence of urticarial edema of the perineural tissue with consequent compression neuropathy have been considered the most plausible explanations for this syndrome.

Because of the proximity of the nerve to the injection site the possibility that the palsy may have resulted from an inadvertently direct into the nerve tissue was considered. In such instances the nerve involvement generally begins shortly after the injection, the paralysis lasts longer and resolves itself gradually and systemic manifestations are invariably absent. The presence of fever, erythematous and petechial eruptions in areas distal to and unrelated to the injection site plus an edematous local reaction typical of immediate-type hypersensitivity all militate against a local nonallergic reaction. Furthermore, the neurologic involvement preceded the local inflammation, favoring an immune response over a nonspecific inflammatory one. To the best of our knowledge this is the first time that tetanus toxoid has been shown to be responsible for this type of neurologic involvement.

Summary

An unusual reaction, peripheral neuropathy, to tetanus toxoid was seen in a 23-year-old medical student. It is believed to be the first recorded reaction of this type following tetanus toxoid administration.

Generic and Trade Names of Drug

Diphenhydramine hydrochloride—Benadryl Hydrochloride.

References


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