Rabies Postexposure Vaccination: Are Antibody Responses Adequate?

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(See the Major Article by Uwanyiligira et al, on pages 201–5.)

The article by Uwanyiligira et al raises an important question concerning poor antibody responders following postexposure rabies vaccination. In a retrospective-prospective study, they found that 5.1% of subjects with potential exposure to rabies had suboptimal neutralizing antibody responses following 4 intramuscular injections of tissue culture vaccine. The study suggests that reducing the current postexposure injections from 5 to 4 may not be sufficient to generate an optimal antibody response. They recommended that antibody levels be determined on day 21.

Current internationally approved tissue culture rabies vaccines have an excellent reputation and must undergo extensive immunogenicity and safety trials before approval. These trials are generally undertaken using healthy young volunteers, often veterinary students [1]. However, such volunteers represent a different population than patients presenting to an animal bite clinic in a country where canine rabies is endemic. Antibody responses are expected to result in titers >0.5 IU/mL on day 14 and to remain detectable for at least 1 year. Studies have also shown that World Health Organization (WHO)—recognized tissue culture rabies vaccines will maintain detectable levels of antibody for at least 21 years in most healthy subjects [2]. Receipt of intramuscular or intradermal boosters is expected to result in a rapidly accelerated antibody response that eliminates the need for immunoglobulin. We are aware of very rare cases of poor response to rabies vaccination in hosts who appeared to be healthy. A laboratory technician who was expected to work with rabies virus was found to be a nonresponder and had to be shifted to another position when several boosters failed to induce antibody (G. M. Baer, personal communication). Very poor or no response to preexposure and postexposure rabies vaccination has been well documented in human immunodeficiency virus (HIV)—infected subjects [3] and is very likely with immunosuppressive drugs; though definitive studies are lacking. Poor or no responses to other vaccines, particularly hepatitis B virus vaccine, are also known [4] and are thought to have a genetic basis.

It would have been interesting to look more closely at the 6 poor responders cited in the Swiss study. A patient’s statement of being in good health should not be accepted at face value in a scientific study, without further critical clinical and laboratory evaluation. A senior animal bite clinic nurse in Bangkok has taken a special interest in ferreting out “hidden” HIV cases associated with rabies exposures. Her work resulted in several publications showing that the immune response is related to CD4 cell counts and can range from poor to no response [3]. A rabies exposure is a major threat to life, and rabies-exposed subjects are entitled to proper evaluation. A quick question or form to complete in a busy emergency department setting may not unearth a history of heavy alcohol or drug abuse, chronic illness, or immunosuppressants.

One apparent purpose of Uwanyiligira and colleagues’ article is to suggest that reducing the number of rabies vaccine injections from 5 to 4 may not be safe, particularly when immunoglobulin is not administered on the first day. We must remember that the same warnings were made when the original Essen regimen deleted the sixth injection, scheduled for day 90 [5]. The Thai Red Cross intradermal schedule also eliminated the 90-day shot in 1995 and has not found it necessary to revise the recommendation [6]. A further reduced intradermal schedule, that can be completed in one week, is now undergoing extensive international field studies and looks promising [7].

A rabies exposure is a severe financial burden for patients and health care providers. Many instances of failure to obtain
postexposure prophylaxis are due to the high cost of vaccines and immunoglobulins. Reducing the cost by reducing the amount of vaccine administered, the travel time to health centers, particularly in rural areas, and the time missed from work would almost surely decrease the numbers of untreated patients and rabies-associated deaths.

Surveillance for persons who do not respond to treatment and a careful analysis of causes of treatment failure should be ongoing worldwide. Creation of an international registry for cases of failure might be appropriate, and such cases should be carefully reviewed for hidden causes. Laboratories that can reliably perform appropriate rabies neutralizing antibody tests are few and absent in many countries where rabies is endemic, and the suggestion to perform routine antibody testing 3 weeks after starting a postexposure regimen will not be possible in most canine rabies-endemic regions. However, it would be important if poor responders could undergo a thorough immunological evaluation to identify causes.

Most postexposure treatment failures are due to deviations from WHO standards and the delayed receipt or nonuse of immunoglobulin [8]. There have, however, been cases of true failure to respond to the standard postexposure rabies prophylaxis recommended by the WHO. The few postexposure treatment failures who were seen at Chulalongkorn University Hospital in Bangkok did not have neutralizing antibody titers detected in serum and spinal fluid specimens collected on admission [9]. The terms “poor antibody responder,” “medium antibody responder,” and “high antibody responder” were first coined by George Baer in the 1980s. It is also becoming increasingly evident that it is not only humoral immunity that protects rabies-exposed subjects. We do not know much about cellular immunity in rabies, but 2 recent rabies survivors had only nonneutralizing antibodies in their sera and no rabies virus RNA [10]. Another study showed that cytokines and chemokines have a function in rabies antibody development following vaccination [11].

All 6 subjects in the Swiss study who had antibody levels of <0.5 IU/mL after 4 intramuscular vaccine injections had a good anamnestic response to boosters. Did they have undetected immune defects from underlying medications or disease? Would they have been at risk if they had been bitten by an infected dog abroad and had not received a booster vaccination as recommended by the WHO? Was their low antibody response due to other unknown causes?

Khawplod et al [12] studied 96 volunteers who were vaccinated in accordance with 6 abbreviated intradermal vaccination schedules, ranging from 0.2 mL given intradermally at 2 sites to the full intradermal postexposure schedule and using Verorab (Sanofi) or purified chick embryo vaccine (Chiron-India). All subjects in all 6 groups had detectable neutralizing antibody responses on day 360 and titers >0.5 IU/mL on days 367 and 374. Sudarashan et al [13] reviewed 66 cohorts of 2799 vaccinees from whom data were collected over 27 years in 6 countries where postvaccination neutralizing rabies antibodies were measured. They studied time intervals between primary and booster vaccinations in individuals who had previously received a full course of preexposure or postexposure prophylaxis and were then reexposed to rabies. The duration of presumed protection by previous vaccination was assessed using a neutralizing antibody level >0.5 IU/mL as a surrogate marker of adequacy. They also found poor response (defined as an antibody titer <0.5 IU/mL) in 0.07% and 0.14% of participants 1 and 3 months, respectively, after primary vaccination. However, all 577 subjects who had previously received preexposure vaccine had antibody responses >0.5 IU/mL 1 and 3 months after primary vaccination [13]. Several Asian countries recommend that no booster is needed if the interval since the last immunization is <6 months (in India and the Philippines) or 1 year (in Sri Lanka). In Thailand, individuals with a severe exposure that is detected within 6 months are often given only 1 booster dose.

What could have caused the poor responses in 6 of the 85 subjects in the Swiss study? Laboratory errors or poor vaccine quality are unlikely. Numbers are small, and the presence of a small cluster of subjects with undetected immunocompromised status is one possibility and, perhaps, the likeliest explanation. If the 6 subjects are still available and willing, they might be called back and evaluated further. The recommendation for routine antibody testing on day 21 is not realistic because of cost and the lack of specialized laboratories in regions of endemicity. Furthermore, most rabies clinicians believe that events during the first week or two after exposure have the greatest influence on survival among patients exposed to rabies. Detection a low or absent titer on day 21 may occur too late to alter the course if rabies is already incubating.

The fact that human rabies immunoglobulin is virtually unavailable in most canine rabies-endemic countries is mentioned repeatedly, and rightly so, in the Swiss article. It was the apparent reason why many cases did not receive human rabies immunoglobulin on initial presentation abroad and why some of these subjects waited for their return to Switzerland before seeking care and starting postexposure prophylaxis. This resulted in a significant delay between exposure and prophylaxis (mean duration, 10 days) and a much increased risk. Fortunately, only a small number of patients presenting to animal bite clinics worldwide have actually been exposed to a rabid animal. They are only rarely available for testing or follow-up. If most had been bitten by a rabid dog, there may well have been deaths among individuals.
in the Swiss study population who did not receive immunoglobulin within a few days of exposure. Travel clinic staff must educate clients who decline preexposure vaccination that modern, highly purified equine rabies immunoglobulins manufactured in France, Thailand, China, and India are available in rabies-endemic countries. These immunoglobulins must be used without delay when human rabies immunoglobulin is not available. They are safe and effective but carry an acceptable small risk of transient serum sickness reactions. Anaphylaxis, common with early crude horse serum products made in the 1970s, is very rare with new purified equine sera, for which the incidence of anaphylaxis is similar to that of penicillins [14, 15].

**Note**

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**References**