

Failure of Postexposure Treatment of Rabies in Children

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Five failures of postexposure treatment of rabies in small children with multiple severe bites on the face and head are discussed. All had received rabies immune globulin and a potent tissue-culture vaccine. However, not all wounds had been infiltrated with immune globulin. Surgical closure prior to wound injection with immune globulin was performed in three cases. Another patient had wounds sutured after an intramuscular injection of immune globulin, without wound infiltration.

There have been previous reports of failures of postexposure treatment of rabies in which tissue culture–derived vaccines and immune globulins had been used [1, 2]. Each of these reported failures resulted in death, and in each case there had been delays in treatment and flaws or omissions with regard to use of current World Health Organization (WHO) treatment guidelines [3]. We present and discuss five such treatment failures involving children who suffered severe face, head, neck, and arm injuries when attacked by a rabid dog. Surgical wound cleansing and primary treatment with rabies immune globulin (RIG) and a series of potent tissue-culture vaccine injections had been started within 3 days following the attacks. A hypothesis concerning possible causes of these treatment failures and recommendations for improvements in the management of cases of severe and multiple bites in small children are presented.

Case Reports

Case 1. A 6-year-old boy was bitten by a street dog in Bangkok in late 1988 and incurred one large, deep facial laceration. His wound was washed and debrided at Chulalongkorn University Hospital on the day of injury. He was given equine rabies immune globulin (ERIG; Institut Pasteur, Paris) at a dosage of 40 IU/kg (total dose, 4 mL [800 IU]), administered intramuscularly into the gluteal region. The wound was not infiltrated with the ERIG. He was then treated with purified Vero cell rabies vaccine (Institute Merieux, Lyon, France), receiving a full intramuscular dose on days 0, 3, and 7. He died of rabies encephalitis on day 12 following the bite. No autopsy was performed.

Case 2. This 9-year-old Thai boy incurred dog bites at 12 sites on his face, head, and arms in 1989 in Chachingsao, Thailand. His wounds were washed and debrided at the local provincial hospital on the same day, and they were injected with 4.2 mL (840 IU, a dosage of 40 IU/kg) of ERIG (Swiss Serum and Vaccine Institute, Bern). All of the ERIG was used to infiltrate wounds as well as possible, but the undiluted volume was inadequate. He then began treatment with the standard WHO-recommended intramuscular regimen of purified Vero cell rabies vaccine [3]. Vaccine was injected into the deltoid region on days 0, 3, 7, and 14, but he died of rabies encephalitis (autopsy-proven by fluorescent antibody testing) on the 25th day after having been bitten. Vaccine and ERIG batches were checked and found potent.

Case 3. A 4-year-old boy was bitten by a stray dog in Galle, Sri Lanka, in October 1993, incurring two large lacerations of his face. Wounds were irrigated within 2 hours of the injury at a local health station. Forty-two hours later he was brought to a hospital. His weight was 9.75 kg, and he was given 200 IU (1 mL) of ERIG into and around the wounds and another 200 IU intramuscularly in the gluteal region, as instructed in the ERIG package insert (Institut Pasteur). The wounds were then sutured under intravenous ketamine hydrochloride anesthesia. Treatment with purified chick embryo rabies vaccine (PCEC; Behring, Marburg, Germany) was started 66 hours following the bite, with use of the WHO-approved "Zagreb" or "2-1-1" intramuscular regimen (1 full dose of vaccine at 2 deltoid sites on day 0, followed by 1 dose each on day 7 and day 21) [3]. On day 21, after the last dose of vaccine was given, it was noted that the child was febrile and drowsy and had weakness in both lower limbs. This was followed by progressive ascending paralysis, respiratory distress, coma, and then death 37 days following the dog bite. Corneal smears and postmortem brain samples were positive for rabies by fluorescent antibody test.

Case 4. A 6-year-old boy was bitten by a stray dog near Bombay, India, in 1991, incurring lacerations on a corner of his mouth, upper lip, scalp, left arm, and calf. The wounds were cleaned and disinfected on the same day, and this was

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followed by suturing under intravenous ketamine hydrochloride anesthesia. PCEC (Behring) was given with use of the conventional WHO-approved intramuscular regimen; one injection was administered on each of days 0, 3, 7, and 14. Human rabies immune globulin (HRIG) could not be obtained until the day after surgery (day 2). One-half of the calculated dose of 20 IU/kg was applied around the wounds, and the rest was injected intramuscularly into the gluteal region, as instructed in the leaflet that came with the HRIG. Fever and inability to swallow were noted on day 16, and the child died of rabies encephalitis the following day. An autopsy was not performed. (This case has been described previously by Fescharek et al. [4]).

Case 5. A 2½-year-old Thai girl was severely bitten on her face by a street dog in Chonburi, Thailand. She incurred three deep lacerations on her right cheek and ear, a wound on the right corner of her mouth, and a wound on her nose. These wounds were immediately cleaned with soap and water, and wound care was repeated before application of povidone iodine 6 hours later. The wounds were then sutured under ketamine hydrochloride anesthesia. She immediately began treatment with the WHO-approved intradermal Thai Red Cross regimen [3, 5] using PCEC (Behring). Two 0.1-mL doses of PCEC were injected intradermally into each deltoid region on days 0, 3, and 7. ERIG (Swiss Serum and Vaccine Institute) was not available until 25 hours after the bite and after surgical closure of wounds, but one-half of the calculated dose of 40 IU/kg (2 mL) was injected around some of the wounds. The rest was given intramuscularly in the gluteal region, as instructed on the insert that came with the ERIG ampule. Fever, sore throat, and inability to swallow developed on day 10, followed by hypersalivation, aerophobia, and then death 7 days later. Her parents did not permit an autopsy.

Discussion

RIG should be given to all patients with severe rabies exposure on the first day of postexposure treatment (severe exposure was defined by the WHO in 1992 as any transdermal wound at any site [3]). This must be followed by a full course of treatment with a potent tissue or avian embryo culture vaccine, administered on an efficacy study-proven schedule [3]. Wound infiltration with RIG is done to neutralize virus before it enters peripheral nerve endings and to stimulate a local T-lymphocyte-mediated immune response prior to the appearance of detectable vaccine-induced neutralizing antibodies 7–10 days later [3, 6–8].

The 1992 Rabies Expert Committee report by the WHO [3], with regard to administration of HRIG or ERIG, states that “as much as possible of the recommended dose [20 IU/kg (HRIG) or 40 IU/kg (ERIG)] should be infiltrated into and around the wounds if anatomically feasible. If any is left, the remainder should be administered intramuscularly in a single dose and followed by a complete course of vaccine.” This is a change from the previous (1984) WHO expert committee

report [7], which on page 31 recommended that “serum should be administered intramuscularly in a single dose.” There is no mention in the 1984 edition of injecting wounds with RIG, in spite of the fact that Dean and Baer had shown in a classic study in 1963 that intramuscular injection of rabies antiserum will not provide a protective systemic level and that local injection of rabies virus-contaminated wounds is essential for survival in cases of severe exposure [8].

Most package inserts that come with immune globulin ampules still (June 1995) recommend giving half of the dose around the wounds and half by deep intramuscular injection into the gluteal region. This old recommendation was never substantiated by published data. Furthermore, it is in direct conflict with the observations of Dean and Baer [8]. The question arises: What does one do if the calculated volume of RIG is inadequate for infiltration of all wounds? Does one give all of the calculated dose of RIG only around the most severe wounds or does one increase the dose (and volume) of RIG? As we have seen in the five instances of treatment failure presented here, this dilemma occasionally involves small children who have been severely bitten at multiple sites (figure 1).

There are no published reports of prospective studies of humans that would give us clear data to answer these questions, and none can be done today. Management decisions will thus have to be made on the basis of logic and clinical experience and reevaluated as more data accumulate. Increasing the dose of ERIG or HRIG in cases in which the calculated volume is inadequate for the infiltration of all wounds has been suggested in Thailand (D. Kingnate, unpublished observation). However, there is evidence that such an increase would suppress the antibody response to vaccination, and the suggestion was therefore rejected [9].

It has become standard practice at the Queen Saovabha Memorial Institute's (QSMI's) animal-bite clinic, at which 30–40 new rabies-exposure patients are treated daily, to administer all of the calculated volume of ERIG or HRIG into and around wounds when necessary. The Tropical Disease Hospital and Bamrasnaradura Infectious Disease Hospital in Bangkok are also following this practice. After case 2 came to our attention in 1989, our staff at the QSMI arbitrarily started to dilute RIG in saline to make up an adequate volume for infiltration of all wounds when the undiluted volume appeared inadequate. Figure 1 shows one of the first patients for whom we diluted the RIG to make up an adequate volume for infiltration. The usual dilutions required to allow infiltration of all wounds in such severe, multiple-bite cases range from onefold to threefold in our experiences. Approximately one such case is seen monthly at QSMI's animal-bite clinic (1 per 1,000 cases).

Another problem is ensuring that infiltration of severe bite wounds on the tips of fingers, where compartments hinder diffusion of infiltrated RIG, is adequate but not damaging. We have encountered one case of minor localized necrosis due to too-vigorous infiltration of RIG into a fingertip. However, this is also an area with many superficial sensory nerve endings



Figure 1. This 26-month-old Thai girl incurred severe dog-bite injuries on her face, scalp, ear, neck, and both arms. The animal was killed and found positive for rabies by fluorescent microscopy. The patient's weight was 14.3 kg. Wounds were irrigated with saline, treated with povidone-iodine solution, and then infiltrated with 3 mL of ERIG diluted threefold in normal saline. She then started receiving purified Vero cell rabies vaccine with use of the Thai Red Cross intradermal regimen, but we doubled the dose and number of sites injected on the first day (0.1 mL intradermally at four sites) [3, 5]. Wounds were repaired by a plastic surgeon 10 days after treatment started; she survived, and the cosmetic result was satisfactory.

and one that is considered to be at high risk of fatal rabies infection. One 11-year-old boy died of rabies in 1987 when a single puncture wound of the finger was not infiltrated with RIG; all of the 40-IU/kg dose had been given intramuscularly in the gluteal region, as was done in case 1 of this series [2]. If a patient with bite wounds arrives after some delay and there is evidence of infection, wound infiltration with RIG is not contraindicated as long as appropriate surgical and antibiotic therapies are applied [10].

All of the five Asian patients described here whose postexposure treatment failed were small children who had incurred severe, multiple dog-bite injuries of the head, face, and arms. All had received WHO-approved potent tissue-culture vaccines and purified tested rabies immune globulins. However, there could not have been an adequate volume of immune globulin, with the dose/volume calculated on the basis of body weight [3], to infiltrate all wounds properly (table 1). In two cases (4 and 5), wounds were surgically closed before being infiltrated with immune globulin. This action could have enhanced spread of virus and of rapid viral entry into peripheral nerves, where viruses are then in an immunoprotected environment [11]. Patient 1 was given RIG intramuscularly and without any wound infiltration. We try to avoid primary suture of animal-bite wounds, preferring to clean and debride them and then

infiltrate them well with ERIG or HRIG. Secondary suture, if necessary, is then performed after 1–2 weeks, when we assume the patient has circulating neutralizing antibodies [9].

Patient 3 had been treated with the abbreviated Zagreb, or 2-1-1, postexposure regimen, which does not provide for a vaccine dosing on day 3 and is not recommended when immune globulin is also indicated [3]. This implies that the Zagreb regimen should not be so used for treatment of patients with category III (severe) exposures to rabies. This schedule is the

Table 1. Examples of volumes of calculated rabies immune globulin (RIG) doses for Thai children, as related to their weight.

Age (y)	Weight (kg)	RIG dose (mL)	
		Equine (ERIG)	Human (HRIG)
2	12.5	2.5	1.7
5	17.6	3.5	4.6
10	24.6	4.9	3.3

NOTE. These are volumes recommended by the WHO and manufacturers on the basis of body weight (40 IU/kg for ERIG and 20 IU/kg for HRIG). ERIG is formulated as 200 IU/mL and HRIG as 150 IU/mL. Weights are averages of children seen at a Bangkok animal-bite clinic. Approximately 30% of Thai dog-bite victims are children <10 years of age.

one most susceptible to antibody suppression by ERIG [9]. We believe that the Zagreb regimen—which is in common use in Europe and is being widely promoted by European vaccine firms in Asia and Africa—should be abandoned, as it provides little advantage over the conventional five-dose intramuscular regimen other than saving one clinic visit and one vaccine dose. If the saving of vaccine (and expense) is the primary objective, we recommend the Thai Red Cross intradermal regimen or the “8-4-1-1” intradermal schedule developed by Warrell et al. [12]. Both have been shown to be highly immunogenic and do not cause significant antibody suppression from RIG administration on day 0. They represent an up to 75% savings in vaccine cost and have allowed many poor countries in which canine rabies is endemic to abandon the use of dangerous nerve tissue-derived vaccines [3, 5, 9, 12–14].

Two of the five cases presented illustrate that HRIG and ERIG are not readily available, even in areas where canine rabies is highly endemic. The high cost of these products (particularly HRIG), however, is only one reason for this shortage. Two major manufacturers of ERIG have recently discontinued production, partly because of the high cost of maintaining a horse farm in Europe. Animal rights advocates have also made the continuing maintenance of one exemplary and historic horse colony for serum production virtually impossible, and this contributed to its recent closure. There is now a worldwide shortage of purified ERIG, the only rabies immune serum product that is affordable in most countries where canine rabies is endemic [13].

Rabies is not retreating as a public health threat. It is still spreading in many regions of the world [15]. Research to create substitutes for RIG has shown that monoclonal antibodies to rabies can be raised [9] and that interferon (and interferon-inducers) could perhaps also be given in place of RIG [9]. It is doubtful, however, that any such products, even if shown to be effective and safe in humans, would replace HRIG or ERIG in the near future. Responsible manufacturers should thus be encouraged not to give up production and export of purified ERIG, which is truly an essential biological.

Increasing the first dose of rabies vaccine and giving it at multiple sites has been shown to result in earlier and higher neutralizing antibody titers than are noted with the conventional five-dose intramuscular schedule [12, 14]. There is also evidence that specific cell-mediated immunity can be demonstrated sooner following multiple-site intradermal vaccine injections [14]. This evidence has led us to double the vaccine dose and sites of injection on the first day when we are confronted with patients whose presentation has been delayed or who have exceptionally severe injuries, such as seen in this series. We offer no data in support of this practice but have started a register of such cases to gather data and evaluate treatment outcomes on a continuing basis.

We suggest that in addition to the three usually recognized categories of severity of rabies exposure [3], a fourth one should be added to represent patients with multiple, severe bites of the face, head, arms, and hands—cases in which the

volume of the calculated dose of immune globulin is inadequate for the infiltration of all wounds. Cases in this new group (category IV) should be managed by dilution of the immune globulin in saline to make up an adequate volume for the careful infiltration of all wounds. Primary suture of such wounds should be avoided if at all possible, but if it is unavoidable, suturing should be carried out only after thorough wound cleansing and injection with immune globulin. K. Bhanganada has studied delayed closure of animal-bite injuries in Thailand and has found a lower incidence of infection than when closure is done shortly after injury; delayed closure, after daily dressing of wounds and appropriate antibiotic therapy, carried a lower risk of infection than did primary repair (K. Bhanganada, unpublished data and [16]). The surgical treatment of severe facial dog bites was also recently reviewed by Morgan et al. [17]. Though no prospective studies have been done to support this practice, it might be justified in such extreme cases to double the initial vaccine dose in an effort to produce earlier and higher neutralizing antibody titers.

Postexposure treatment of rabies is wasteful since many patients worldwide are given expensive vaccine and immune globulin although they may not be infected. Staff members at QSMI estimate that a majority of animal-bite victims presenting for treatment in Thailand actually have not been infected with rabies virus. Most have injuries inflicted by dogs and cats that are not available for observation or examination and may or may not have had rabies. Meticulous attention to treatment guidelines issued by the WHO [3] is, nevertheless, mandatory when one is confronted with a patient who has been bitten by a mammal in a rabies-infected region. Better control of dogs and their regular vaccination remain the primary measures for combating rabies worldwide.

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