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Rabies post-exposure prophylaxis in malnourished children exposed to suspect rabid animals

G. Sampath[a,*], S. Parikh[b], P. Sangram[a], D.J. Briggs[c,1]

[a] *Institute of Preventive Medicine, Narayanaguda, Hyderabad 500 029, India*
[b] *Aventis Pharma, Mumbai, India*
[c] *Department of Diagnostic Medicine, Kansas State University, Manhattan, KS, USA*

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Abstract

Over half of the world's malnourished children live in Asia where more than 90% of reported human rabies deaths occur. In order to determine the effect of malnutrition on the immune response to rabies post-exposure prophylaxis (PEP), 45 children with moderate to severe protein energy malnutrition (PEM) who were exposed to potentially rabid animals were enrolled in a clinical trial. Patients received purified chick embryo cell rabies vaccine (PCECV) on days 0, 3, 7, 14 and 30. Blood was drawn on days 0, 14 and 30 and evaluated for the presence of rabies virus neutralizing antibody. All children that met the protocol criteria developed rabies virus neutralizing antibody titers above the acceptable level of 0.5 IU/mL by day 14 and no serious adverse events were reported. We conclude that children in this study that received four or five doses of rabies vaccine intramuscularly developed an acceptable immune response despite their severe degree of protein energy malnutrition.

Keywords: Rabies; Malnourishment; Post-exposure prophylaxis; Protein energy malnutrition

1. Introduction

Rabies and malnutrition might at first seem to be unrelated, but in fact both are connected in several ways. For example, both are life-threatening medical conditions that are entirely preventable, both affect the same populations of economically disadvantaged persons living in tropical developing countries that have limited financial resources for food and healthcare, and children under the age of 15 are particularly vulnerable to both conditions [1–4]. The World Health Organization (WHO) has indicated that over 90% of the global human rabies deaths are reported from Asia and approximately 45% of these victims are children under the age of 15 [1]. Concurrently, UNICEF and other foundations have reported that in Asia, approximately 50% of pre-school age children suffer mild to moderate malnutrition [2–4].

The threat of rabies in Asia is directly related to the fact that the disease is endemic in the millions of unvaccinated stray and community dogs that live on the continent. Conservative estimates indicate that over 7 million patients receive post-exposure prophylaxis (PEP) annually in this region of the world [5]. Children are at greatest risk of exposure because they are frequently the victims of animal bites (most often dogs) due to their small size, playful nature, and their tendency to provoke animals, including those that could be infected with rabies. When attacked, children often experience multiple bite injuries in highly innervated areas like the scalp, face and upper parts of the body, as well as hands and fingers. Exposures in these anatomical regions can reduce the incubation period of rabies thus increasing the risk of contracting the disease [6]. Additionally, if they receive a minor

* Corresponding author. Tel.: +91 40 27567893; fax: +91 40 27560191.
E-mail addresses: gadeysampath@yahoo.co.uk (G. Sampath), briggs@vet.ksu.edu (D.J. Briggs).
[1] Tel.: +1 404 638 6609; fax: +1 785 532 4474.

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bite, children may choose not to tell their parents for fear of punishment and because they might want to avoid the series of painful injections of nerve tissue vaccine that is commonly used in the anti-rabies treatment centers in many developing countries of Asia.

The WHO recommendation for PEP includes prompt wound care, a five dose series of a modern tissue culture rabies vaccine accompanied by the administration of rabies immune globulin (RIG), the dose of which is determined by the weight of the patient [7]. Unfortunately, in most Asian countries that have a high prevalence of both rabies and protein energy malnutrition (PEM) in children, the complete WHO recommended PEP regimen is rarely administered due to a lack of affordable tissue culture vaccines and an extremely limited availability of RIG. Currently, RIG is only available in a few large urban centers in Asia and as a result, very few of the millions of exposed patients receive this life-saving drug [8]. To help protect children and reduce the need for RIG, WHO has recommended that children living in canine rabies endemic countries (where rabies is not well controlled) should be considered for pre-exposure rabies immunization [7,8], since individuals previously immunized against rabies with tissue culture vaccines, do not require RIG on re-exposure. A similar recommendation for pre-exposure vaccination has been utilized very effectively in North America for populations at increased risk of exposure to rabies, such as veterinarians, veterinary students, animal control workers etc. [7,9]. However, in developing countries the use of pre-exposure vaccination is not widespread due to a general lack of awareness of the availability of this approach to protection against rabies as well as the high cost of implementing a widespread vaccination program in children.

Studies examining the immune response to vaccination in children suffering from PEM have reported varying results according to the type of vaccine administered [10–13]. For example, antibody response to typhoid, BCG, and in some cases polio vaccine has been reported to be depressed in children with severe PEM whereas measles vaccine appears to be efficacious even in malnourished children [10].

The increased risk of exposure to rabies, high number of rabies deaths, and large number of children suffering from PEM in Asia, warrants an investigation into the immune response to rabies vaccine in children suffering from PEM. Therefore, the following study was conducted to evaluate the humoral immune response to PCECV in children exposed to suspect rabid animals and suffering from PEM that presented at a large anti-rabies treatment center in Asia.

2. Materials and methods

2.1. Patients

All children that participated in the study were patients at the rabies clinic at the Institute of Preventive Medicine in Hyderabad India (where over 46,000 patients receive PEP annually) and all had experienced WHO Category II or Category III exposures to suspect rabid animals. All patients involved in the study were evaluated by a physician prior to enrollment in the study. Patients met the inclusion criteria if they were between the ages of 6 months to 16 years, had a known exposure to a suspect rabid animal and satisfied the Indian Academy of Pediatrics (IAP) criteria for PEM. Patients were excluded if they had a prior history of rabies vaccination, were suffering from an acute infectious disease, had received anti-malarial drugs within the previous two months, and/or had received parenteral or oral steroids or immunosuppressive drugs within the previous two months. The age, weight, and height of each child were recorded before the first dose of vaccine was administered. All children that received at least four doses of vaccine were included in the per-protocol population. All patients were examined for adverse events by the attending physician within 30 min after vaccine was administered. Additionally, parents were interviewed on subsequent visits to determine if children experienced any adverse events after vaccine administration.

2.2. Informed consent

The protocol of the study was reviewed and approved by the ethics committee of the Institute of Preventive Medicine in Hyderabad. The study protocol was explained and informed consent was secured from all parents of the children in the study prior to enrollment.

2.3. Vaccine

All patients received purified chick embryo cell rabies vaccine (PCECV) produced in Ankleshwar India by Chiron Vaccines. The vaccine production facility in Ankleshwar has been inspected and approved by WHO and meets all of the criteria for rabies vaccine production of a modern cell culture rabies vaccine. All vaccines used in the study had a potency of $\geq$2.5 IU/dose as required by WHO.

2.4. Protein energy malnutrition evaluation

The nutritional status of each patient was evaluated based on the IAP classification system for identifying malnourished children. Four grades of malnourishment, based on the percentage of standard weight for age, as recognized by the IAP were utilized in the study [14], Grade I: children between 71 and 80% of the normal percentage of standard weight for age; Grade II: children between 61 and 70% of the normal percentage of standard weight for age; Grade III: children between 51 and 60% of the normal percentage of standard weight for age; Grade IV: children below 50% of the normal percentage of standard weight for age.

2.5. Post-exposure prophylaxis

Patients were scheduled to receive five doses of PCECV administered intramuscularly as recommended by WHO [1].