Case Report and Literature Review

A Case of Serious Adverse Reaction Following Rabies Vaccination

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Abstract

Introduction. Rabies is one of the most deadly infectious disease. We present a challenging case of an adverse reaction following rabies vaccine in a child. Case Summary. A 10-year-old girl was bitten by a stray dog in Bali and was prescribed rabies post-exposure prophylaxis. She developed breathlessness, abdominal cramps, and lips and eyes swelling 30 minutes after the second dose of rabies vaccine. The subsequent vaccine was successfully administered as a graded challenge with premedication. The final dose was administered in entirety under close observation. She developed transient hypotension 30 minutes later, which spontaneously resolved. Conclusion. There were multiple challenges in the care of this pediatric patient who was potentially exposed to rabies and experienced systemic adverse events during the course of post-exposure prophylaxis. A thorough clinical assessment should be made to weigh benefits versus risks of proceeding with rabies vaccination, bearing in mind that the disease is deadly.

Keywords
adverse reaction, rabies vaccine, purified chick embryo cell vaccine (PCECV), purified vero cell rabies vaccine (PVRV), children

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Introduction

Rabies is one of the most deadly infectious disease that has a high case fatality rate. It has a worldwide distribution with few exceptions, such as Japan, Antarctica, and Singapore.1 Singapore has been rabies-free since 1953. This is accomplished through various measures imposed by the Agri-Food and Veterinary Authority of Singapore, including strict import conditions and quarantine requirements on animal imports from rabies-affected countries. The Agri-Food and Veterinary Authority of Singapore makes it compulsory for dog owners to obtain a license and microchip for their pet to allow easy tracing and identification for rabies control. To deal with any potential outbreaks, there is also a ready stockpile of rabies vaccination.2

The rabies virus is transmitted through exposure to saliva from an infected animal bite, such as dogs, bats, skunks, raccoons, and cats. Rabies is endemic in dogs in most South-East Asian countries and is most commonly transmitted to humans via rabid dog bites.3 It can also be

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transmitted from inhalation of aerosolized rabies virus, tissue and organ transplants, or where broken skin or mucous membranes come into contact with any infected body fluid, whether humans or mammals.4

We present a case of serious adverse reaction to the rabies vaccine, which was administered as part of the rabies post-exposure prophylaxis (PEP).

Case Report
A 10-year-old girl with background of allergic rhinitis and well-controlled asthma was bitten by a stray sick-looking dog in Bali, Indonesia. She sustained a superficial 1.5-cm linear wound on the dorsum of her right hand, corresponding to a grade 2 exposure according to the World Health Organization category of contact.1 She did not previously receive rabies vaccination. She received day 0 rabies vaccine with a purified vero cell vaccine (PVRV) in Bali and developed abdominal cramps and rash shortly after. This subsequently resolved in 2 days. On return to Singapore, she was given second dose (day 4) of rabies vaccine with a purified chick embryo cell vaccine (PCECV) and developed generalized weakness, a sensation of breathlessness, abdominal cramps, and lips and eye swelling 30 minutes later in a General Practitioner clinic. On arrival in the Children’s Emergency, her vital signs were stable, cardiorespiratory system examination was unremarkable, and there was no eye and lip swelling or rashes. Her symptoms resolved with antihistamines. As per our hospital’s rabies PEP protocol, she was due to receive 1 dose of human rabies immunoglobulin (RIG) before day 7 as well as rabies vaccine on days 0, 3, 7, 14, and 30. She was given human RIG on day 5 for which she tolerated well with no reactions. However, the day 7 rabies vaccine dose was omitted as she had complaints of occasional abdominal pain, headache, vomiting, and periodic generalized weakness. These symptoms gradually resolved over a few days. For her day 14 rabies vaccine dose with PCECV, she received premedication with intravenous diphenhydramine and a graded dose challenge comprising 0.1 mL, 0.4 mL, and 0.5 mL. She was kept under close monitoring for 2 hours. No adverse reactions were reported apart from drowsiness from the premedication. The fourth rabies vaccine dose with PCECV was given on day 21 in view of the missed day 7 dose. After discussion with the parents, premedication was omitted. An anesthetist as well as standby medications such as adrenaline were readily available. She developed hypotension around 30 minutes after the vaccine was given with the lowest blood pressure (BP) recorded at 72/45 from 104/60. The subsequent BPs recorded returned gradually to normal baseline. The BP was recorded every 5 minutes, with a printout obtained of the improving trend over 20 minutes. There were no symptoms of dizziness or syncope reported with this drop in BP as the child was reclined in the hospital bed. She was subsequently monitored for a few hours after the vaccine and was discharged with minimal symptoms reported. The child remains healthy a year later at review in clinic and did not develop any signs or symptoms of rabies.

This study was approved by the SingHealth Centralised Institutional Review Board (Reference Number: 2012/340/E). Written consent was obtained from the patient’s parents for publication.

Discussion
Rabies is caused by a number of different species of neurotropic viruses in the Rhabdoviridae family, genus Lyssavirus, and there is a predilection for neural tissue. The World Health Organization estimates a total of 30 000 to 70 000 deaths per year worldwide with up to 95% of these deaths occurring in developing countries such as Africa and Asia. Bali is a popular tourist destination that still faces rabies as a major public health problem. Rabies is distributed in all districts of Bali and was responsible for 135 human deaths from 2008 to 2011.6

Of note, 40% of people bitten by suspected rabid animals are children under 15 years of age.3 Children are more susceptible to animal bites due to their attraction to animals, lack of safety awareness, and reluctance to report bites or scratches. They are also smaller size and tend to be more susceptible to being bitten in the face, head, and hand, which decreases the incubation period of the rabies virus on infection.3

The initial incubation period for rabies is typically 1 to 3 months. However, this may vary from 1 week to 1 year as it is dependent on factors such as location of virus entry and viral load. Once infected, patients may present with initial prodromal symptoms such as fever, nausea, headache, and giddiness, accompanied with paresthesia around the wound site. They then go on to develop either encephalitic (“furious”) or paralytic (“dumb”) rabies.8 Encephalitic rabies develop in around 80% of people infected, displaying signs and symptoms of hydrophobia, aerophobia, and autonomic instability. Paralytic rabies is seen in less than 20% of people infected, and they present with ascending paralysis, mimicking Guillain-Barré syndrome. Subsequent paralysis of muscles of respiration leads to death.

The only proven effective rabies prophylaxis9 to date is pre-exposure prophylaxis as well as prompt PEP consisting of wound care, RIG, as well as multiple doses of rabies vaccine. There are 2 main types of vaccines available, nerve tissue vaccines and cell culture–derived vaccines.10,11 The use of nerve tissue vaccine from rabies virus–infected goat or sheep brain tissue has led to severe
adverse reactions and are currently being phased out in developing countries. Cell culture–derived vaccines include the human diploid cell vaccine (HDCV), PCECV, PVRV, and purified duck embryo vaccine. Of these, PCECV and PVRV are more commonly available in developing countries due to its low cost and they are as effective and safe as HDCV.\textsuperscript{7,10} Rabies vaccination is given in 4 or 5 intramuscular 1 mL dosages together with RIG for patients who have not been previously vaccinated and were exposed to an animal bite injury (5 doses in immunocompromised patients).\textsuperscript{12} However, adverse events resulting from administration of the rabies vaccine can pose a challenge to the treating clinicians as there is a need to weigh the risk of contracting the deadly rabies disease versus the potentially life-threatening systemic reactions to the vaccine. There has been an increasing number of patients receiving rabies vaccine in our unit over the past 5 years, from 18 patients in 2013 to 64 patients in 2017. There was no previous serious adverse event due to rabies vaccine reported in our unit.

Most reported adverse events following immunization with rabies vaccine are local reactions such as pain at the injection site, swelling, redness, and induration. According to the US Centers for Disease Control and Prevention,\textsuperscript{9} local reactions are more common following HDCV (60% to 89.5%) as compared with PCECV (11% to 57%). Most local reactions were mild and resolved spontaneously in a few days. Systemic reactions such as fever, dizziness, headache, and gastrointestinal symptoms were reported in 6.8% to 55.6% of recipients of HDCV versus 0% to 31% in PCECV. According to the US Vaccine Adverse Events Reporting System (VAERS), there were 30 adverse events per 100,000 doses of PCECV distributed and 3 serious events per 100,000 doses distributed. Serious events included 13 neurological events and 20 hospitalizations. These were described in 24 (7%) of reports. According to the VAERS, “there was no pattern among the 13 neurological adverse events suggesting a plausible relationship to vaccination.” Also, there were a total of 20 adverse events that were classified as possible anaphylaxis, with 3 serious adverse events.\textsuperscript{7,13}

Of note, a large comparison study on adverse reactions of PCECV and PVRV done by Ramezankhani et al\textsuperscript{14} showed 1 incident of hypotension reported in the PCECV arm (n = 747) and none in the PVRV arm (n = 702). However, this is not statistically significant, and the study did not include children less than 5 years of age. Another study done in China compared the safety and immunogenicity of PVRV and PCECV in patients with animal bite exposure. It showed no significant difference in safety and immunogenicity in the 387 patients who received either PCECV or PVRV. However, the study found that more systemic adverse reactions occurred in patients aged <5 years with lower rabies virus neutralizing antibody titers in both groups.\textsuperscript{15} Our patient received PVRV first followed by PCECV, as subject to availability in the respective countries. Their contents were similar apart from the host system used. No thiomersal was present in both vaccines. She developed hypotension with PCECV and had lips and eye swelling with generalized weakness. This is similar to the study done by Ramezankhani et al.\textsuperscript{14} However, this comparison is limited as she was not seen after PVRV was given in Bali, hence no actual comparison can be made based on her clinical status.

The US Advisory Committee on Immunization Practices\textsuperscript{9} state that “once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually such reactions can be successfully managed with anti-inflammatory, antihistaminic, and antipyretic agents.” However, in the event that a patient develops hypersensitivity to rabies vaccine, close monitoring and pretreatment with antihistamines can be considered together with graded dosages of the vaccine, as well as switching between vaccine types to reduce the risk of another reaction.

Following a recent publication on the International Consensus (ICON)\textsuperscript{16} on allergic reactions to vaccines, awareness of a patient who develops an allergic reaction to a vaccine warrants careful eliciting of previous history of allergy that might put them at risk for other vaccinations. This includes previous allergy to other vaccinations or if there are other known allergies, such as an egg allergy. Subsequently, the clinician should decide if future doses of the vaccine are truly needed. This entails weighing the risk-benefit ratio of preventing rabies versus a risk of an adverse reaction to the vaccine, noting that systemic side effects from PCECV rabies vaccine can be common, up to 31% reported.\textsuperscript{9}

**Conclusion**

This case highlighted the importance of having a systematic approach to adverse reactions to rabies vaccine. Clinicians should be watchful of adverse effects in prescribing rabies vaccination especially in patients with a history of allergic conditions. In a child with suspected adverse reactions following rabies vaccine, a thorough clinical assessment should be made to weigh benefits versus risks of proceeding with rabies vaccination, bearing in mind that the disease is deadly.

**Author Contributions**

ZK: Contributed to design; contributed to acquisition, analysis, and interpretation; drafted manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy.
WCC: Contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

SHO: Contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AENG: Contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

KCT: Contributed to acquisition, analysis, and interpretation; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

NWHT: Contributed to conception; critically revised manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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