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Rabies transmission risks during peripartum – Two cases and a review of the literature

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ABSTRACT

We report two cases of probable rabies in near-term/at-term pregnant women in sub-Saharan Africa and Asia. One baby was delivered by caesarean section and the other one vaginally. Both received post-exposure prophylaxis (PEP), including RIG and vaccine and both are alive and healthy, at 9 and 24 months, respectively.

We found 14 other published cases of infants born from rabid mothers. One confirmed case of rabies transmission occurred. The other children born from rabid mothers, with or without caesarean section, did not acquire rabies, and were still healthy at the time of reporting, with or without post-exposure prophylaxis.

Mother-to-child transmission of rabies is possible, but rare, because rabies virus is not present in blood and exposure of the baby's mucosa to maternal infectious fluids and tissue seems limited. A conservative approach should however, be adopted, and rabies PEP, including RIG, be administered as soon as possible to babies born from probably rabid mothers. Whether cesarean-section clearly provides prevention remains unclear.

Rabies can be prevented in pregnant women by PEP administration. Rabies cell-culture vaccines are safe and effective and can be administered to pregnant and lactating women, as well as newborns. Efforts must focus on raising rabies awareness in the general population, as well as in healthcare workers.

1. Introduction

Q2 Rabies is a zoonotic and neglected disease caused by lyssaviruses, rabies virus (RABV) representing a major public health issue in endemic countries. Human infection usually occurs through a transdermal bite or scratch by an infected animal, a domestic dog in over 99% of documented human rabies cases [1]. The incubation period is typically 1–3 months but may vary from <1 week to >1 year [2]. RABV causes an acute, progressive encephalomyelitis. Although rare cases of survival have been reported in patients exposed to bat rabies who developed a vigorous, early immune response, rabies due to canine RABV is almost always fatal: attempts to treat symptomatic patients infected with dog RABV variants with therapeutics and intensive care support usually fail [3].

Prevention of clinical disease is nearly 100% effective, even after confirmed exposure to RABV: Post-exposure prophylaxis (PEP), consisting of immediate and extensive cleaning of the wound after exposure, and a course of vaccines meeting WHO recommendations, with rabies immunoglobulin (RIG) if indicated, is highly effective in preventing rabies, saving countless lives each year [1,2,4,5].

Rabies remains prevalent in developing countries. According to recent estimates [6–8], canine rabies still causes around 59,000 deaths and over 3.7 million disability-adjusted life years (DALYs)

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each year; this is five times the fatalities reported during the 2004–2005 Ebola epidemic in West Africa [9]. The greatest risk of developing rabies falls upon the poorest regions of the world, especially in rural areas of Africa and Asia [1,6,8], where vaccination of domestic dogs is not widely implemented and where access to PEP is most limited or unaffordable for target populations [10].

It is inevitable that in such settings some victims bitten by suspected rabid animals will be pregnant women and that some will progress to rabies in the absence of timely and effective administration of PEP. Every rabies case is an avoidable tragedy, but when rabies occurs in a pregnant woman, the life of the future baby is also compromised. If rabies symptoms occur in an at-term pregnant woman - when nothing can be done to save the mother - the issue is whether and how the newborn can be saved. There are no relevant specific guidelines and little data to guide clinicians. We report two cases of probable rabies in at-term pregnant women and their outcome, one in sub-Saharan Africa and one in Asia. We have also reviewed and analysed the available data on similar cases, in an attempt to identify best practices in such situations.

2. Case reports

2.1. Case 1–Benin, Africa

On 16 February 2015, a pregnant seamstress aged 25 (nulliparous primigravida), was referred to the Comé hospital, 80 km from Cotonou, the economic capital of Benin, for mental disorders of acute onset. She presented agitation, persecutory delusions, excessive sweating and hydrophobia. Thirty days earlier, she had been bitten on the left leg (Grade III exposure) by a puppy that had immediately been put down, without *post-mortem* laboratory testing for of canine rabies. The patient had received tetanus antitoxin and a "black powder" prepared by a traditional healer from ashes resulting from incineration of the biting puppet's tail. She did not receive any PEP.

The patient was transferred to the Gynaecology-Obstetrics University Clinic of the HKM National University Hospital in Cotonou for suspected rabies. Because of the strong suspicion of rabies and as the pregnancy was at full term (39 weeks of amenorrhea), it was decided to perform an emergency caesarean delivery. The patient received 10 mg diazepam IM and 20 mg diazepam IV to allay anxiety and agitation, and the C-section was performed under classical general anaesthesia with tracheal intubation. A male child was extracted. Every effort was made to avoid contact between the mother's extraplacental tissues or fluids and the baby's mucous membranes (amniotomy after extraction of the head). The amniotic liquid was meconial. After suture of the uterus (hysterorraphy) and abdominal closure, the mother was transferred to the intensive care unit. She then progressed over a period of 4 days to febrile paraparesis, followed by paraplegia then tetraplegia requiring intubation. She died in the intensive care unit 5 days after delivery. Autopsy was denied by the relatives and the placenta could not be analysed due to traditional cultural norms in Benin. The case was notified to the health authorities.

The baby weighed 3370 g and measured 54 cm at birth. He was delivered in a state of apparent death, with an APGAR score of three at the first minute; but he rapidly improved and his APGAR score was six at the fifth minute, and 10 at the 10th minute. He was fed with infant formula and grew well, with no symptom suggestive of rabies.

Due to logistical constraints (problems in vaccine and RIG procurement, compulsory authorization from the father who had to find resources for his transportation to Cotonou), it was 13 days before the newborn received rabies vaccine IM (Essen protocol at Days 0, 3, 7, 14 and 28 – vaccine: Verorab Sanofi Pasteur, batch K 1394-2) as well as equine RIG (Favirab Sanofi Pasteur, batch S 7046). All injections were delivered to the anterolateral aspects of the thighs. Tolerance was good, with a short fever episode (38 °C). The child is alive and in good health at 7 months.

2.2. Case 2 – Cambodia, Asia

Early on October 8, 2013, a 33 year-old woman from Kompong Chhnang Province, Cambodia, presented to the local rural health centre with fever, hydrophobia and inability to drink, aerophobia, restlessness and difficulty breathing and sleeping. A couple of hours earlier, she had given birth to a healthy boy at her home, by vaginal delivery. Symptoms suggestive of rabies had progressively appeared during the 12 h preceding delivery.

Three months earlier, in early June 2013, while she was 5 months pregnant, she was bitten by a 3 month-old puppy on the second toe of the right foot and on the exterior aspect of the right ankle (Grade III exposure). The puppy appeared sick and bit another person (a child, no bleeding at bite site, lost to follow-up). It was put down and not laboratory-tested. The wound of the pregnant bite victim was cleaned using brake fluid and lemon. She received neither rabies PEP nor tetanus prevention.

On admission at the local health center, she received IV saline and was immediately referred to the Maternity ward of Kompong Chhnang Provincial Hospital, with mention of "hydrophobia". There, she received Ringer lactate infusion and diazepam and was referred to the Calmette reference hospital in Phnom Penh, the capital city, for suspected rabies. On arrival at the Calmette hospital on October 9, 2013, she was diagnosed as a probable rabies case according to WHO definition [11]. She was neither further examined nor sampled for laboratory confirmation and was sent home, as no treatment can prevent death from rabies and death at home is preferred in Cambodia for cultural, religious and financial reasons. She died later that morning.

On October 9, the epidemiology staff of the Institut Pasteur Cambodia (IPC) was informed by contacts in Kompong Chhnang of this probable perinatal exposure to rabies. IPC requested the local health staff to perform a mouth swab on the corpse of the mother before traditional cremation, to obtain a *post mortem* saliva sample. The swab was tested at the IPC virology laboratory (rabies reference center) using an in-house reverse-transcriptase polymerase chain reaction assay, with primers well-suited to the region [12]. The sample tested negative but this result remained questionable because of the clinical presentation, the very poor quality and insufficient quantity of the sample and the lack of demonstrated validity of this type of sampling [13]. The case was notified to the health authorities.

IPC staff examined the newborn in Kampong Chhnang on October 10, 2013 (48 h post-delivery) and administered PEP, injecting 0.66 ml of Favirab equine RIG (lot J8427 exp. 08.2014) in the gluteal muscle + 0.1 ml ID in each deltoid area with Verorab rabies vaccine (lot J1316-2 exp. 05-2015) following the modified Thai Red Cross schedule. The health center staff who had cared for the mother were immunized against rabies, as well as relatives who were to provide care for the newborn.

After written informed consent by the father, blood and saliva from the baby were sampled, at 7 days and at 1 month. All tests were negative. The child is currently alive and well at 24 months.

2.2.1. Review of the literature

We performed a comprehensive search of other published cases of infants born to rabid mothers. Results are summarized in Table 1.

The outcomes of our two cases are discussed together with data from the published cases, in an attempt to gather evidence on the