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A confirmatory death case of human rabies in Bangladesh

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ABSTRACT

In the present study clinical profile with specific attention to typical clinical presentation and deficiencies/lacunae in post-exposure prophylactic management as per WHO guidelines in adult rabies patients. An observational analysis was performed on a clinically suspected human rabies case, whose samples were gathered at a rabies diagnostic laboratory at Infectious Disease Hospital, Dhaka (IDH) over the course of three days (20/09/2021 to 23/09/2021). The patient's clinical and demographic information was acquired. The clinical specimens involved cerebrospinal fluid (CSF), saliva, nuchal skin biopsy and serum collected antemortem, and brain tissue obtained post-mortem. A variety of laboratory tests were used to make the diagnosis. The patient died in hospital 3 days after hospitalization (20 days after the occurrence of animal bite). After referring the patient to the IDH, a lumbar puncture was administered, and PCR tests for rabies were forwarded to the cerebrospinal fluid (CSF) and serum. The serum & CSF have indicated antibodies with rabies. The fluorescence microscopy screening program for rabies was positive in the brainstem, cerebral cortex, cerebellum, and cerebrum. The patient's samples of saliva (0.5-1 mL) and skin were also sent to PCR for rabies. Diagnostic testing of the patient later confirmed human rabies. Human rabies is a crucial health problem. So, there are required to educate the community and health workers about the value of immediate and adequate post-exposure treatment, to launch an effective control program for rabid dogs, and to make availability of rabies vaccine as well as rabies immunoglobulin (RIG).

KEYWORDS: Dog bite, rabies, human rabies, Bangladesh

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INTRODUCTION

Rabies is a widely spread viral disease with a death pace of about 100 percent in humans (Willoughby Jr *et al.*, 2005; Takayama, 2008). Lyssavirus tends to cause rabies, which further causes acute viral encephalomyelitis (Depani *et al.*, 2012). Internationally, approximately 59,000 fatalities been spotted while approximately 15.69 million people are susceptible to rabies every year (Hampson *et al.*, 2011; Depani *et al.*, 2012). Rabies remains a vital public health threat, particularly in developing nations of Africa and Asia, representing over 95% for every century of all types of human rabies (Fooks *et al.*, 2014; WHO, 2021). Rabies is a non - communicable disease with rabies-related deaths between several vulnerable and poor populations not often reported (WHO, 2021). Since human vaccines and immunoglobulins are not readily accessible or

available, they have been identified as the cause of the high mortality rate of the human rabies.

Nearly 99% of rabies infection in humans is related to the bite or scratch of rabid domestic dogs, while wild creature transmission, for example, bats, foxes, wolves, emerges to have been reported (Gongal & Wright, 2011; Depani *et al.*, 2012; Johnson *et al.*, 2014). The usual incubation time for rabies is 01 to 03 months, but it can also fluctuate from less than a week to over a year based on age, bite area, and human viral rabies load (Abbas & Kakkar, 2013; WHO, 2021). Two aspects of human rabies clinical manifestations have been observed: paralytic and furious rabies. Furious rabies accounts for approximately 67 percent of cases of rabies and is characterized by hyperactivity, nervous behavior, hydrophobia, aerophobia, delirium, reduced vision, and occasional seizures. Paralytic rabies accounts for approximately

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thirty-three percent of cases of human rabies, causing loss of motion of the appendages and respiratory muscles (Depani *et al.*, 2012; WHO, 2021). Death occurs within 5-7 days after the beginning of symptoms when human rabies is not treated. Rabies treatment can prolong patients' survival span by 133 days (Willoughby Jr *et al.*, 2005). In human rabies cases, deaths will in general be because of cardiac arrest (Heymann, 2008). There seem to be currently no specific tests that can prove infection with the rabies virus in humans ever since clinical disease begins. Using different diagnostic techniques, the identification of viral antigens, whole viruses, or nucleic acids in infected tissues (brain, skin, urine, or saliva) will confirm human rabies during the clinical and post-mortem stage of the disease. Even though the laboratory diagnosis of rabies systemic infection is difficult after a viral infection, prophylaxis post-exposure has aided to decrease the risk of contamination with deadly rabies virus in such an exposed individual (Warrell & Warrell, 2004; WHO, 2005).

Post-exposure prophylaxis for rabies means rinsing and washing the bite or scratch site with soap, detergent and water, and an antiseptic as well as rabies immunoglobulin (RIG) administration. In Bangladesh, rabies is common, whereas cases of human rabies are under-reported in other developing countries (Hossain *et al.*, 2011). Furthermore, veterinary services in here are often limited in the diagnosis of rabies, since Sellers' stain and fluorescent antibody testing, commonly used techniques for rabies diagnosis, are mostly unavailable. A person gets attacked by a dog frequently affirms the medical diagnosis of human rabies by the veterinary practitioners if a dog shows symptoms for rabies. In Bangladesh, prevention and control initiatives aimed at decreasing the prevalence of human rabies have been directed at increasing dog vaccination against rabies, wild dog elimination, neutering, and delivering human pre-exposure or post-exposure vaccines. However, recently we encountered a history of certain death of a young man who gets dog bites. He later developed encephalopathy with observable human rabies antibodies in the CSF, thereby stressing the importance of clinical evaluation.

MATERIAL AND METHODS

Clinical Samples

During the study period, clinical samples from the patient with probable human rabies were obtained. The clinical specimens involved cerebrospinal fluid (CSF), saliva, nuchal skin biopsy and serum collected antemortem, and brain tissue obtained post-mortem. The referring clinicians were advised to fill out a standardised case history form containing demographic and clinical information, as well as the patient's history of animal exposure and post-exposure management (PEM). All human samples (antemortem and post-mortem) utilized in this work were sent to the Neurovirology laboratory for diagnostic confirmation of rabies in clinically suspected cases.

Laboratory Methods

Serum and CSF samples involved in this study were analyzed for rabies virus neutralising antibody (RVNA) titres by rapid

fluorescent focus inhibition test (RFFIT), using a method described previously (Narayana *et al.*, 2014). Nucleic acid extraction (NAE) followed by TaqMan real-time PCR targeting the nucleoprotein (N) gene using a method narrated previously was performed on brain tissues, saliva, nuchal skin biopsy, and CSF samples, for identification of rabies viral RNA (Mani *et al.*, 2014). The Fluorescent Antibody Test (FAT) was also used to identify rabies nucleoprotein antigen in brain tissues (Dean & Abelseth, 1973).

RESULTS

Case Presentation

On August 23 2021, a twenty-five-year-old young male was attacked by a puppy sustaining a category III wound on his left ankle. He was taken to a local clinic, where his wound was cleansed and he was given the rabies vaccination. Despite the fact that the man had a category III wound, rabies immunoglobulin was not administered as recommended. The man resided in Dhaka, Bangladesh, which had a high incidence of rabies and dogs at the time. The individual was taken to a general practitioner on September 16, 2021, because he was lethargic, and experiencing a lack of appetite and confusion. The man was given non-specific treatment including an enema at home without improvement. The individual was taken to Dhaka's Infectious Disease Hospital (IDH) on September 20, 2021, with fever, confusion, headache, anxiety, and a lack of muscle coordination with spasms. At the time of admission, the patient had received human rabies immunoglobulin intravenous infusion along with Ribavirin 1000 mg q6h IV, a dose of human diploid cell vaccine (HDCV), but also interferon, analyzing the concern for human rabies. He was artificially ventilated as the seizures were intense and were administered diazepam and subsequently pancuronium bromide. He had to be medicated with morphine because the spasms became intractable and started to deteriorate his health status.

A possible diagnosis of rabies was considered due to the history of puppy's bite and the clinical presentation of the patient, despite the vaccination history. Clinical samples and details of patient outcome were available with laboratory-confirmed rabies (Tables 1 and 2). The patient's antemortem samples included serum, CSF, saliva, and nuchal skin biopsy. The patient's post-mortem brain tissue was received for laboratory confirmation. On the patient's samples, real-time TaqMan PCR was used to identify rabies viral RNA. The CSF, saliva, and nuchal skin biopsy samples confirmed positive for real-time TaqMan PCR.

Table 1: Clinical details of the patient with laboratory-confirmed rabies and known disease outcomes

| | |
|--|-----------------|
| Age in years | 25 |
| Sex | M |
| Type of rabies (paralytic/encephalitic/atypical) | Encephalitic |
| Incubation period | 28 days |
| Animal and site of bite | Dog; Left ankle |
| PEP (vaccine/RIG) | 2 doses; No RIG |
| Outcome | Died |
| Period of Survival | 3 days |

Table 2: Results of laboratory tests in patients with laboratory-confirmed rabies and known disease outcomes

| | |
|---|-----------------|
| Samples | 1 st |
| RVNA titres by RFFIT IU/ml | |
| CSF | 7.5 |
| Serum | 15 |
| Detection of viral RNA by real-time PCR | |
| CSF | POS |
| Saliva | POS |
| Nuchal skin | POS |
| Brain tissue | POS |

Post-mortem brain tissue of the patient, which tested positive for rabies using both FAT and real-time TaqMan PCR. CSF sample was positive for RVNA titre (7.5 IU/ml) by RFFIT, indicating rabies encephalitis. Serum sample tested was positive for RVNA titre (15 IU/ml).

Symptoms such as inability to swallow, hydrophobia, and photophobia have been vigorously increased in the patient afterward. So, the patient was taken to the Intensive Care Unit (ICU) on day 3 of hospitalization. The general condition of the patient worsened after being transferred to the ICU and the patient suffered from cardiac and respiratory arrest having wide fluctuations in temperature and blood pressure. The family agreed to withhold advanced medical assistance, and the patient died on September 23 shortly afterward. The rabies virus was removed via postmortem from brain tissue. In the end, after 3 days of hospitalization, the patient died in the hospital.

DISCUSSION

It is approximated that rabies causes 59,000 deaths across over 150 countries annually, with 95 percent of cases appearing in regions of Asia and Africa. The whole number is likely a reasonable approximation of the true burden of the disease due to extensive underreporting and uncertain estimates. 99% of cases of rabies are dog-mediated and the disease risk is overwhelmingly faced by rural poor communities, with nearly half of cases due to children under 15. Western Europe, Canada, USA, Japan, and several Latin American countries have abolished dog-mediated rabies (WHO, 2018). The subcontinent, which comprises India, Pakistan, and Bangladesh, has the world's biggest rabies problem in the world (Baer, 1988).

There is one case study of a chicken (*Gallus domesticus*) that acquired rabies after being bitten by a rabid dog (Baby et al., 2015). Other than bites, inoculation modes for the virus include exposure to mucous membranes or broken skin through licks, aerosol transmission (bat-infested caves), and organ transplantation. After the virus is introduced through the muscles because of a bite, the virus enters the nerve endings and moves to the central nervous system (CNS) through the axoplasmic flux. Once it reaches CNS, clinically manifested as diffuse encephalopathy occurs viral replication and further dissemination to the periphery. Not every person bitten by an out-of-control animal will get the disease developing.

If a rabid wolf bites more than one human and one of them dies, 60 percent of the remaining wolf bites may develop the disease (Hattwick & Gregg, 1975). The case that discussed here had suggestive symptoms of furious rabies, confirmed by PCR. The patient eventually died within 03 days of the beginning of acute nervous symptoms. Based on the history of the patient obtained and unverifiable data, the patient didn't clean the injured area with soap and water after an animal bite did occur. In this scenario, a vicious dog bite happened to lead to the patient's death due to inadequate action that made the treatment plan unsuccessful. Previous studies have reported that rabies-related mortality typically happens following animal bites due to non-referral or delayed referral to health centers. More than seventy-five patients suffering from rabies died at home. Hossain et al. estimated that every year 166,590 people are bitten by animals in Bangladesh [95% confidence interval (95% CI) 163,350-170,550] Bangladesh's annual incidence of deaths from rabies was estimated at 1.40 (95 percent CI 1.05-1.78)/100,000 population. By concluding this, we approximated that 2100 (95 percent CI 1575-2670) people in Bangladesh die every year because of rabies (Hossain et al., 2012). Rabies remains a crucial issue in the field of public health in Bangladesh. While rabies is a horrifying, deadly, and incurable illness, it can be avoided 100 percent and the health system is still not treating it properly.

CONCLUSION

Bangladesh is a rabies-endemic area, and only physicians here thoroughly review the animal bite cases. We found that the numbers of cases of animal bites and human rabies in Bangladesh are beyond current levels. In all the cases, there are some common similarities seen in the patients with rabies and that is - they do not take proper care of their wounds due to poor knowledge, lack of access to a physician, financial constraints, and the lack of adequate post-exposure prophylaxis (PEP). Veterinarians, medical staff, and wildlife biologists will need to work together to resolve animal bites issues more quickly. Access to appropriate health care facilities and improved public awareness are also required to prevent the deaths of rabies in Bangladesh.

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Conflict of Interest

The authors declare that they have no competing interests.

Ethical Approval

No personal details or identifying information are included in this article. Consent was provided by the patient for the case report to be written and published. Ethics approval was not obtained from the authors' Institutional Ethics Committee because it was not required for a case report.

Authors' Contributions

MJC, JH, SGJ, MZAH, TA, LCS, and SH conceived and designed the study, conducted research, provided research materials, and collected and organized data. MJC, JH, and SGJ analyzed and interpreted data. MJC, MZAH, TA, LCS, and SH wrote the initial and final draft of the article, and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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