

Rabies viral encephalitis with probable 25 year incubation period!

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Abstract

We report a case of rabies viral encephalitis in a 48-year-old male with an unusually long incubation period, historically suspected to be more than 20 years. The case was referred for histological diagnosis following alleged medical negligence to the forensic department. The histology and immunocytochemical demonstration of rabies viral antigen established the diagnosis unequivocally. The case manifested initially with hydrophobia and aggressive behavior, although he suddenly went to the bathroom and drank a small amount of water. History of dog bite 25 years back was elicited retrospectively following clinical suspicion. There was no subsequent history to suggest nonbite exposure to a rabid dog to consider recent event causing the disease, although this cannot be totally excluded.

Key Words

Long incubation period, Negri bodies, rabies, viral antigen

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Introduction

Rabies continues to be a fatal zoonosis in humans, accounting for nearly 20,000 deaths per year in India. Although the classic variants of rabies, the hydrophobic/furious form and paralytic/dumb rabies are well recognized, the disease is at times mistaken for other entities, especially early in the clinical course and the diagnosis being established by postmortem examination after death. In rabies, the incubation period (the interval between exposure and the first symptom in prodromal period) is more variable than any other acute infection. During the incubation period, it is suggested that the virus is probably sequestered in the skeletal muscle at the site of bite and amplified during this time, while the exposed person remains asymptomatic.^[1-3]

Majority of the cases have an incubation period between 31 and 90 days. In the literature, the overall reported incubation period varies from 30 days in 30% of the cases, 31–90 days in

54%, greater than 90 days in 15% and in 1% of the cases beyond 1 year is recorded.^[3] In a cohort of 47 cases studied following autopsy at a single center in South India, the median incubation period recorded was 60 days (range 7 days to 4 years).^[4]

A case of rabies in a Vietnamese girl who immigrated to Australia was reported, with the incubation period exceeding 6.5 years.^[5] The preliminary genetic analysis of the viral genome in this case suggested likely origin from Southeast Asia.^[6] Although incubation periods as long as 14 years and 19 years are on record,^[7,8] it was felt that the theoretical possibility of another recent insignificant exposure to the virus-carrying animal vector could not be ruled out completely. Viral molecular epidemiological studies provide insight into the migratory pattern of the virus-carrying animal and human vectors,^[9] but not the mechanism of viral latency.

We report an unusual case of rabies, with very prolonged incubation period suspected to be more than 20 years, from the South Western state of India, Goa.

Case Report

A 48-year-old male was admitted to the Goa Medical College Hospital in November 2009, with the history of fear of water and air. He gave a definite history of dog bite 25 years ago (at the age of 23 years) on the leg and no other contact with known rabid canine subsequently. He could not provide history

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of vaccination or medical attention at that time. During the clinical examination, he was anxious and scared at the sight of water, flow of air under a fan and had photophobia, as noted by the medical residents and consultants. Two days after admission, suddenly, he went to the bathroom, washed his face and drank a glass of water. The photophobia and aerophobia had reduced. He was conscious, alert and well oriented to time and space and did not have laryngeal stridor or pharyngeal spasm. He had no previous history of any neurological illness or seizure disorder prior to admission to this hospital. Although the features of hydrophobia and photophobia suggested rabies encephalitis, he had a well-maintained consciousness level with no neurological deficits and the act of drinking water cast doubt on the diagnosis and he was referred to the general hospital for further management. However, he went to a private hospital in the zone. Within a few hours, he had hematemesis and he aspirated and succumbed. Following the allegation of medical negligence by the guardian because of sudden deterioration and death, the body was shifted to the Forensic Department at Goa Medical College to establish the cause of death.

A medicolegal autopsy was conducted, which revealed stress ulcers in the stomach with hemorrhage and aspiration pneumonia. The rest of the parenchymal organs and the vasculature were normal. The brain was submitted for neuropathological examination at the specialty center.

Gross examination of the brain did not reveal any pathology, other than congestion of meninges and brain. The grey and white matter of the cerebral and cerebellar hemispheres, cerebellum, the deep nuclear masses and the ventricular system in the brain were normal. Histological examination revealed dense perivascular lymphocytic cuffing in the leptomeninges and brain parenchyma and microglial nodular aggregates in the grey matter, suggesting an encephalitic pathology. Many discrete, eosinophilic, intraneuronal Negri bodies were noted in the neurons, especially in the frontal and temporal cortex, hippocampus and cerebellar Purkinje cells [Figure 1a]. The inclusions could be specifically immunolabeled with antibody

to nuclear capsid protein of rabies virus thus establishing the definitive diagnosis of rabies encephalitis [Figure 1b]. No further virological and molecular genetic studies of the viral genome could be carried out as the brain was submitted in 10% formalin after fixing for 1 week by the forensic pathologist.

The past history of the deceased was traced retrospectively. He hailed from the Northern districts of Karnataka (South India) and migrated with his family to Goa in search of livelihood more than 25 years back. He settled in a semiurban area in Goa and did not travel to distant places. With proactive assistance of the Director of Health Services, In-charge – Integrated Disease Surveillance Project, Epidemiological Cell, Directorate of Health Services, Panaji, Goa, the available past history was collated. The deceased used to deliver milk to a number of households in the area. He was a lover of dogs and used to caress them. The information gathered from the local residents of the housing colony where the deceased stayed revealed a history of lifting two stray dog carcasses from the roadside by the corporation/panchayat workers for burial, corresponding to the period the deceased was bitten (1984–1985). No further relevant information was available from the family members or the Directorate of Animal Husbandry and Veterinary Services. There was no history of dog bite to any other individuals in the colony at that time. The deceased subsequently worked as a household assistant for many years in the past. During this time, there was no history of coming in contact with a suspected rabid dog. He remained asymptomatic and healthy until he presented suddenly with symptoms suggestive of rabies and succumbed in 2 days.

Based on the available evidence in this case of rabies encephalitis, the incubation period was tentatively considered to be 25 years from the time of dog bite. The area he lived all along was not considered a habitat for bats, to suspect the remote possibility of bat rabies. The possibility of the deceased having come in contact with an infected canine or having a nonbite exposure during its asymptomatic phase cannot be totally ruled out, although positive history was not forthcoming.

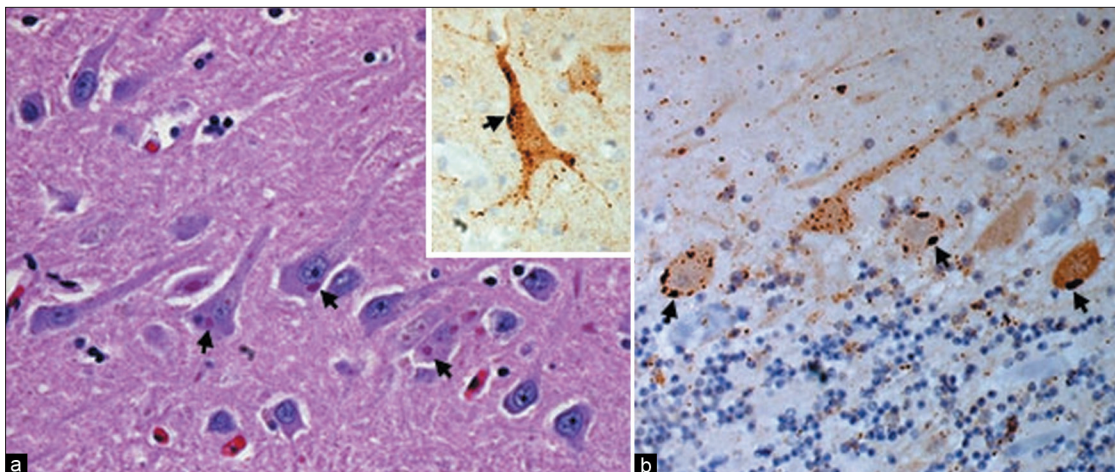


Figure 1: (a) Section from the hippocampus reveals numerous intracytoplasmic eosinophilic Negri bodies within the cytoplasm of Ammon's horn neurons (arrows, a). Abundant rabies viral antigen is seen accumulating within the cytoplasm of the neurons on immunostaining (inset a, arrow). (b) Rabies viral nucleocapsid antigen is also seen accumulating as variably sized rounded deposits within the Purkinje neurons of the cerebellum (arrows), corresponding to Negri bodies, with spread along the apical dendrites into the overlying molecular layer (a: HE $\times 200$, inset: Immunoperoxidase $\times 200$; b: Immunoperoxidase $\times 200$)

In the cohort of 47 cases autopsied at our Institute, the history of dog bite was not available in 13 cases.^[4] Generally, it is assumed that the exposure to canine bite/licking might have occurred so long before the onset of symptoms that the event was forgotten or considered unimportant. However, in the present case, the deceased, prior to death, was alert, conscious and well oriented in time and space with normal cognition. He gave a definite history of dog bite dating back to 25 years. There was corroborating official information of lifting dead dogs from the colony he lived in, which is a circumstantial evidence of canine rabies in the colony corresponding to the time of the stated dog bite. Finding dead street dogs in a human habitat corresponding to the time of history of unprovoked dog bite of human subjects is considered probable evidence of rabies infection among the canines in the colony. These dead dogs are cleared from the street by health authorities as a general practice without autopsy to establish definitive diagnosis for various administrative, logistic and economic reasons anywhere in India. Hence, definite epidemiological data on canine rabies in different geographical areas is not available, except for research on small samples at veterinary colleges and universities. Hence, we tend to believe that the tentative incubation period for rabies in this case was unusually long (nearly 25 years). To the best of our knowledge, this is probably the longest incubation period recorded. Attempts at molecular epidemiological analysis of the rabies virus isolated from the brain of the deceased after fixing in formalin were not pursued for technical reasons.

We wish to suggest that giving credence to the actively forthcoming clinical history from a cognitively sound and conscious patient before death correlating with pathological diagnosis and acknowledging the rare cases of rabies with long incubation period is essential to further the knowledge about the phenomenon of very long incubation in cases of rabies encephalitis, although the evidence in the present case is, to an extent, tentative. The anatomical site of viral latency and the mechanism of reactivation of rabies, a neurotropic virus, remains an enigma to be unraveled.

However, we would like to reiterate that rabies can also be transmitted by nonbite exposure like licking or minor scratch causing breach to the skin by an infected canine in the asymptomatic stage. Usually, these events are considered

insignificant and appropriate immunoprophylaxis is not sought by the victim, finally ending with fatality.

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