Nipah virus infection with cerebellar dysfunction

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ABSTRACT

Background: The Nipah virus (NiV), known to exist in various fruit bats, is associated with one of the deadliest infections affecting human beings. The virus has caused outbreaks in Malaysia, Singapore, Philippines, Bangladesh, and the West Bengal state of India. Pigs were the intermediate hosts during the Malaysian and Singaporean outbreaks and horses in Philippines; while the Indian and Bangladesh outbreaks saw a bat to human followed by human-to-human transmission. The infection is characterized by rapidly progressive encephalitis and acute respiratory distress syndrome, carrying a very high mortality rate.

Case Presentation: We present the case of a middle-aged male who presented with fever, vomiting and loose stools, and throat pain. His initial blood investigations were normal. He later developed diplopia, cerebellar symptoms, and segmental sweating. His blood, urine, and throat swab tested positive for NiV. He was started on antivirals but succumbed to death.

Conclusion: NiV infection, in humans, presents with a wide spectrum of clinical manifestations, ranging from asymptomatic infection to acute respiratory infection and fatal encephalitis. It is transmitted to humans from animals, such as bats or pigs, or contaminated foods. This was our first experience with NiV; and probably one of the first reported cases from our region. Our experience showed the occurrence of cerebellar symptoms in NiV infection.

Keywords: Nipah virus, Paramyxoviridae, encephalitis, cerebellar dysfunction, acute respiratory distress syndrome, ribavirin.

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Background

Paramyxoviridae is a family of enveloped helical RNA viruses and are responsible for majority of acute respiratory infections, including Measles and Mumps. The genera included in the family are - Respiro-, Morbilli-, Rubula-, Avula-, and Henipavirus, and a group of yet to be classified viruses. Henipavirus contains two of the most pathogenic viruses known in humans, Hendra and Nipah virus (NiV), causing zoonotic outbreaks in various parts of Asian continent. The 'Malabar' region of the southern state of Kerala experienced an outbreak of NiV infection for the first time in 2018. The patient being reported is one of the initial cases of the outbreak with an unusual presentation.

Case Presentation

A 55-year-old male presented with high grade intermittent fever, watery loose stools (5–6 episodes) and non-projectile vomiting, and throat pain of 3 days duration. He was not a known case of any comorbid condition and was not on any regular medications. He was febrile (101°F) with other vitals being stable. An aphthous ulcer was present over the soft palate. His systemic examinations were normal. Blood investigations like complete blood count, liver and renal functions and urine microscopy were normal. He was started on oral Clarithromycin (500 mg twice daily). Blood and throat swab cultures were sterile. Chest X-ray was also normal. Epstein Barr Virus VCA (Viral Capsid Antigen) IgG antibody was positive.

On day 3 of admission, he developed binocular horizontal diplopia on gaze to right, suggestive of right lateral rectus muscle weakness. There were no signs of meningeal irritation and ophthalmic examination was normal. Computed tomography of brain and cerebrospinal fluid analysis were also normal. Ceftriaxone (1 gram twice daily) was added along with intravenous methyl prednisolone (500 mg once daily). Patient continued to have fever spikes (101°F to 102°F).

The following day morning, he became unsteady due to bilateral cerebellar dysfunction. Bilateral finger nose test was abnormal and gait ataxia was present. There was no nystagmus, and by night, he became disoriented and displayed myoclonic jerks involving both lower limbs and right upper limb. Segmental sweating was also noted over upper trunk. He also developed dyspnoea (saturation 90% with 10 liters oxygen). Chest examination revealed bilateral crackles and arterial blood gas analysis showed severe respiratory acidosis. Repeat chest X-ray had patchy opacity over right middle and lower zones, suggestive of acute respiratory distress syndrome (ARDS) (Figure 1). He was intubated and put on mechanical ventilation. Intravenous acyclovir (15 mg/kg q8h), meropenem (500 mg q8h), and fosphenytoin were added to his medications.

In view of his quick worsening and neurological manifestations, the possibility of NiV was considered. His blood, urine, and throat swab specimen were sent for NiV

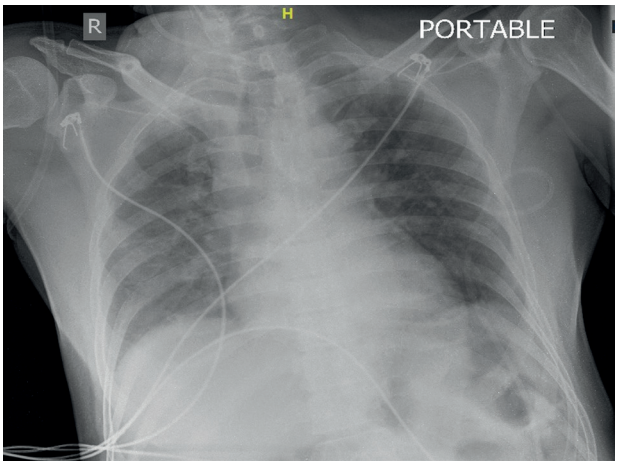

Figure 1. *Chest X-ray showing heterogenous opacity involving right middle and lower zones suggestive of ARDS.*

virological study by real time polymerase chain reaction (RT-PCR) (on day 8 of illness). His urine tested weakly positive for NiV, while throat swab and blood were negative. Repeat blood culture samples were again sterile. Antiviral was changed to oral ribavirin (2-g loading dose followed by 4 g/day in divided doses).

On day 8, his blood pressure rose to 200/120mm Hg. Electrocardiogram showed sinus tachycardia and echocardiogram was normal. On day 9, he developed hypotension requiring inotropic support (with dopamine and noradrenaline). Repeat blood, urine, and throat swab samples (sent 4 days after the initial sample) tested strongly positive for NiV. He expired on day 14 (i.e., 17th day of illness). The timeline of events have been outlined in Table 1.

Discussion

NiV belongs to Henipavirus genus of Paramyxoviridae family. Pteropus bats, popularly known as flying foxes or fruit bats, are the natural reservoirs of the virus. The first incidence of the NiV was reported simultaneously in pigs and humans in Malaysia in years 1998–1999 [1]. The name was derived from Kampung Sungai Nipah or Nipah River Village, where the virus was first isolated. Pigs were the intermediate hosts displaying symptoms of infectious respiratory and neurologic disease [2].

The changes in ecological conditions, in the form of urbanization and deforestation, have led to the emergence of NiV into the pig population and subsequently into the human population. The establishment of pig farms in Malaysia within the territory of the natural host led to the introduction of the virus into the pig population; with subsequent spread in southern Malaysia and Singapore. The direct contact with pigs (which act as amplifying host) or fresh pig products was responsible for the transmission of the virus to humans [3].

In Philippines, the virus to human transmission was thought to be due to direct exposure to infected horses, consumption of undercooked meat of infected horses, or from contact with contaminated body fluids while slaughtering the infected horses [4].

The outbreaks in Bangladesh and India were believed to be either due to direct contact with bats or by contact with material contaminated by them like date palm sap. The Bangladesh outbreaks have identified different routes of transmission like climbing trees (probably contaminated with infected date palm sap), contact with sick persons, and contact with sick animals.

The NiV infection is characterized by severe, rapidly progressive encephalitis, carrying a high mortality rate [5]. The symptoms usually occur within 3 to 14 days of exposure, with an incubation period ranging from 5 to 14 days. However, an incubation period as long as 60 days has been reported [6]. Malaysia and Singapore witnessed severe febrile encephalitic disease [7]. Fever, headache, dizziness, and vomiting were the main symptoms. More than 50% of the patients had decreased consciousness and brainstem dysfunction [5]. The same was the situation in Bangladesh resulting in very high case fatalities [8]. In India, there were two outbreaks. The first occurred at Siliguri, West Bengal during the year 2001, affecting 66 people with acute encephalitis and resulting in 45 deaths. Fever, headache, vomiting, altered sensorium, myalgia, respiratory distress, and involuntary movements or convulsions were observed. Patients were normotensive on admission and later developed hypertension prior to death [9]. The second outbreak took place in Nadia district of West Bengal. Fever, headache, and myalgia were the main presenting complaints. Some also had episodes of vomiting, disorientation, respiratory distress [10]. In Philippines, majority patients presented with encephalitis, while others had influenza like symptoms and meningitis [4].

The diagnostic tests include virus isolation, nucleic acid amplification tests, and serology [11]. Virus isolation and RT-PCR from throat and nasal swabs, cerebrospinal fluid, blood, and urine should be performed during the early course of the disease. In later stages, antibody detection by ELISA (IgM and IgG) can be used. In fatal cases, immunohistochemistry on tissues collected during autopsy should be performed to confirm the diagnosis. The standard test for detection of anti-NiV antibody is serum neutralization test [12].

The treatment is mainly supportive care; with no medications or vaccines available as of now. Ribavirin, a broad spectrum antiviral, can cross the blood brain barrier and may be useful to reduce the mortality in cases of acute NiV encephalitis and the duration of ventilator support [13]. m102.4, a neutralizing human mechanical antibody, that recognize the receptor binding domain of the NiV G glycoprotein has been successfully tested in animal model [14]. Favipiravir, a purine analogue that inhibit viral RNA-dependent RNA polymerase, shows promising results in NiV infection [15]. Various studies have shown that balapiravir may be active against NiV.

Table 1. Timeline of events.

DAY	EVENT
0	Fever, watery loose stools and non-projectile vomiting, throat pain
3	Presented to hospital
6	Developed binocular horizontal diplopia on gaze to right
7	Gait ataxia, segmental sweating over upper trunk
8	ARDS – Intubated and put on mechanical ventilation Urine for NiV (RT-PCR) – Weakly Positive Blood and throat swab specimen for NiV (RT-PCR) – Negative Oral ribavirin started
11	Accelerated hypertension
12	Repeat Urine, blood and throat swab specimen for NiV (RT-PCR) – Strongly Positive
13	Hypotension requiring inotropic support
17	Expired

The risk of bat to human transmission can be reduced by decreasing bat access to date palm sap and by boiling freshly collected date palm juice. Bat bitten fruits should be avoided. All fruits should be washed thoroughly and the skin should be peeled before eating. The risk of human-to-human transmission can be reduced by avoiding close contact with infected patients. Heath care workers and those taking care of infected individuals should use gloves and personal protective equipment. Regular hand washing is mandatory. Disinfection of the equipment and environment, and proper waste management is essential in preventing transmission. Protective clothing and gloves should be worn while handling sick animal and their tissue in order to reduce the risk of animal to human transmission.

The patient being reported was our first experience with NiV. Unlike the usual findings of leucopenia and thrombocytopenia, our patient had a normal complete blood count. Cranial nerve paralysis, especially ptosis, brain stem dysfunction evidenced by hypertension, tachycardia, segmental sweating, and nystagmus were observed in the Malaysian outbreak; but cerebellar dysfunction was an unusual manifestation which was seen in our case. The patient described was one of the initial cases which marked the beginning of the NiV outbreak of May 2018 in the "Malabar" region of Kerala state in India. However, early diagnosis, robust infection control measures along with adequate and proper barrier methods helped to curtail the outbreak rapidly.

Conclusion

NiV in humans presents with a wide spectrum of clinical manifestations, ranging from asymptomatic infection to acute respiratory infection and fatal encephalitis. Fruit bats are the natural reservoirs of NiV. The virus can be transmitted to humans from animals (such as bats or pigs), or contaminated foods. Human-to-human transmission is also possible. The primary treatment for humans is supportive care. There is no treatment or vaccine available for either people or animals. Ribavirin may be useful in acute NiV encephalitis.

List of Abbreviations

NiV	Nipah virus
VCA	Viral Capsid Antigen
ARDS	acute respiratory distress syndrome
RT-PCR	real time polymerase chain reaction

Consent for publication

Obtained from Wife as patient expired.

Ethical approval

Yes (since this is not a research work, only verbal approval was obtained with importance to patient bystander consent).

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Summary of the case

1	**Patient (gender, age)**	Male, 55
2	**Final diagnosis**	Nipah virus infection with cerebellar dysfunction
3	**Symptoms**	Fever, loose stools, vomiting, throat pain, gait ataxia
4	**Medications**	Ribavarin
5	**Clinical procedure**	-Antiviral Meication
6	**Specialty**	Internal Medicine, Neurology