

A Case Series on the Recent Nipah Epidemic in Kerala

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Abstract

During May 2018 there occurred an outbreak in Kerala, which started in Soopikkada Village, Changarothu Grama Panchayath in Perambra Taluk, Kozhikode district, of a febrile illness with altered sensorium and ARDS. The diagnosis was made from the second case that it is the dreaded nipah infection. Following that 18 cases tested positive for nipah virus infection of which 2 survived. Also there were four deaths with similar clinical picture but which occurred before the virus was identified. They were considered as probable cases.

Bangladesh epidemic recurs yearly in small cohorts.²

Here we are elaborating the clinical picture of 10 cases of the outbreak in Kerala of which six were positive for nipah infection and four cases were probable nipah cases including the index case who was admitted and treated in Govt Medical college Calicut.

Introduction

Human Nipah virus was first isolated in Malaysia in 1998.¹ It produced mild disease in pigs but 300 human fatalities. Then there occurred outbreaks in

Bangladesh starting from 2001 onwards the source of most of which could be traced to fruit bats and ingestion of date palm sap contaminated by secretions from bats. Even though the epidemic did not recur in Malaysia the

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Table 1: The important clinical features of all the ten patients

Clinical features	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Age (years)	26	49	48	23	48	27	19	32	75	25
Sex (M/F)	M	M	F	F	M	M	F	F	F	M
Incubation period (days)	Not known	10	12	8	7	7	10	9	6	7
Fever	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sore throat	No	No	No	No	No	No	No	No	No	No
Myalgia	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Headache	Yes	No	No	Yes	No	No	Yes	No	No	Yes
Vomiting	Yes	No	No	Yes	No	No	Yes	Yes	No	No
Altered sensorium	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Seizures	Yes	No	No	No	No	No	Yes	No	Yes	No
Cranial nerve palsy	No	No	No	No	No	No	No	No	No	Ptosis b/l
Hypotonia	No	No	No	No	No	No	No	No	No	No
Meningism	Yes	No	No	No	No	No	Yes	No	No	No
Cough	No	Yes	Yes	Yes	No	No	Yes	Yes	No	No
Hemoptysis	No	No	No	No	No	No	No	Yes	No	No
Loose stools	Yes	No	No	No	No	No	No	Yes	No	Yes
Chest X-ray	n	No	Fluffy	ARDS	Not taken	Normal	Bl fluffy	b/l infiltrates	Not taken	No
Trop I	Increased	No	Increased	Increased	Elevated	No	N	Elevated	Normal	No
Thrombocytopenia	Yes	Yes	No	No	Yes	No	Yes	Yes	No	No
Hypertension	No	No	No	No	No	No	No	No	No	No
Respiratory distress	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes
Autonomic dysfunction		No	Yes	No	No	No	No	No	No	Yes

Cases

Case 1

The first patient which is the index case is a 26 year old male, electrician by profession with no previous comorbidities who presented to MCH casualty with history of Fever head ache vomiting and diarrhoea for 5 days and cough with breathlessness for 1 day. He was initially admitted

in Perambra government hospital and was then shifted on 5/5/2018 to Govt Medical College Calicut. There was No h/o diplopia, drooping of eye lids, seizures, deviation of angle of mouth or h/o paucity of limb movements. No h/o body rashes or travel outside Kerala or h/o insect bite. On examination, Patient was drowsy, disoriented in time place and person, but there were no focal neurological deficits or signs

of meningeal irritation. His vital signs were stable. Since the patient had fever and altered sensorium the provisional diagnosis of encephalitis was considered first. A possibility of fever and vomiting and possible metabolic encephalopathy was also thought of. Investigations revealed normal total count with 6300 cells/mm³, mild thrombocytopenia, and normal renal and liver function tests.

The dengue serology as well as a rapid malarial test was negative. Patient was started on antibiotics and antivirals. By evening patient become tachypnoeic, breathless. On examination patient had coarse crackles over bilateral lung fields with a fall in oxygen saturation. ABG showed hypoxia and ECG showed sinus tachycardia. A provisional diagnosis of acute respiratory distress syndrome was made. Patient was intubated and ventilated. But soon patient developed cardiorespiratory arrest and succumbed to the illness about 8hrs after his admission. The final diagnosis at the time of death was viral encephalitis with ARDS.

Case 2

49 year old male who was admitted 10 days after the death of index case. He had no comorbid illnesses previously. He was earlier admitted at Perambra general hospital with 7 days h/o fever and cough at a time when the index case was admitted there. He received parenteral antibiotics and was discharged. 5 days later fever reappeared with fatigue and head ache when he went to nearby Balussery general hospital from where he was detected to have thrombocytopenia and was referred to here on the next day. On arrival to our centre he was conscious oriented but bystanders complained of increase talkativeness for 1 day. His PR was 124/min and BP 130/90 mm of mercury, spo2 90% in room air. Respiratory system examination revealed bilateral fine crepitations. Investigations then revealed leucopenia, thrombocytopenia. ECG showed normal sinus rhythm. Dengue serology was negative. Renal and liver function tests were negative.

About 12 hrs after his admission patient's altered sensorium worsened and he also developed respiratory distress. Chest auscultation revealed basal crepitations and oxygen saturation dropped to 80% in room air. He was intubated and ventilated. Endotracheal tube suction showed bloody secretions. He was given acyclovir as antiviral drug thinking of the possibility of viral encephalitis. He also received antibiotics and other supportive measures. But in spite of all emergency resuscitative measures patient couldn't be revived and he succumbed to the illness about 24 hrs after his admission.

Case 3

48 year female with no history of comorbidities was admitted with fever and myalgia of 1 week duration and headache. There was no history of breathlessness or dyspnoea or cough. On examination she was febrile, tachypnoeic and blood pressure was high (200/110 mmhg). The system examinations were normal. Her investigations revealed normal complete blood count, renal and liver function tests. Within 5-6 hrs of admission her tachypnoea worsened her oxygen saturation dropped and she developed bilateral basal crepitations and was ventilated. ECG taken then showed sinus tachycardia, chest x ray revealed bilateral fluffy opacities. At the same time troponin I was highly elevated and a bedside echo revealed global left ventricular dysfunction. Meanwhile she was started on broad-spectrum antibiotics, oseltamivir and other supportive measures. Her dengue serology was negative. Her blood pressure then came down and she had to be started on ionotropes and finally in spite of all resuscitative measures she succumbed to her illness 12 hrs after admission with a diagnosis of unspecified viral fever with myocarditis and acute respiratory distress syndrome.

Case 4

23 yrs. old female from Thennala, Malapuram with no previous comorbidities presented with complaints of fever for 6 days, abnormal movements of upper limbs and altered sensorium for 2 days. Patient had diffuse type headache from onset of fever itself. No h/o seizures or vomiting. Patient developed altered sensorium on 5th day of fever. She also had abnormal movement of head and both upper limbs and vomiting episodes along with altered sensorium. There was no history of urine incontinence or pain/diarrhoea/ constipation/ rashes.

On examination she was stuporous and tachypnoeic. She had tachycardia, tachypnoea and saturation fall. Her Pupils were bilaterally sluggishly reacting and mid-dilated. The plantar reflex were bilaterally mute. There was no neck stiffness. The striking feature was involuntary movement involving left upper limb. there were bilaterally scattered crepitations Patient had desaturation and worsening of

tachypnoea, hence invasive mechanical ventilation support given. Her routine investigations were normal with no thrombocytopenia. But her troponin I levels were strikingly high. Patient ABG showed respiratory acidosis. Chest X-ray showed ARDS pattern. ECG-sinus tachycardia. CSF study was normal. Patient went for refractory hypotension and condition deteriorated. Patient expired despite all supportive measures given. Patient had visited MCH Calicut during may 1st week, hence suspecting nipah samples sent post-mortem for nipah screening. Her urine, endotracheal tube secretions came positive for nipah viral PCR.

Case 5

48 year old male with diabetes, chronic kidney disease developed carbuncle and fever for which he was admitted in a local hospital and incision and drainage was done. From there on the sixth day of illness he developed altered sensorium and was referred to here. At admission he was stuporous and soon developed dyspnoea and respiratory system examination revealed bilateral fine crepitations. He was soon ventilated, started on broad spectrum antibiotics, antivirals and other supportive measures. But his general condition worsened and succumbed to his illness 24 hrs after admission. His investigations revealed a total count of 9400 cells/mm³ with predominant polymorphs and urine routine showed plenty of pus cells. His ECG showed sinus tachycardia and troponin I was very much elevated (172). In view of the possibility of pulmonary embolism a Dimer was done which was normal. The final diagnosis was ARDS, acute on chronic kidney disease type 2 diabetes mellitus and urinary tract infection. The possibility of sepsis was considered but could not explain the rapid worsening. A blood sample for nipah was sent which was positive.

Case 6

27-year-old male presented to the casualty with fever, cough, headache and myalgia of 1-day duration. He had history of contact with index case on 5/5/18 and his wife also expired due to nipah infection (case 4). On examination, patient was conscious and oriented, febrile, had tender and enlarged cervical lymphadenopathy. System examination was normal.

There was no neck stiffness or no focal neurological deficits. As he had strong epidemiological link, samples were sent for nipah PCR analysis and throat swab came out to be positive. Patient was started on ribavirin, antibiotics and other supportive measures. Hospital stay was uneventful and patient improved within 2 days. Repeat NIPAH RT-PCR was done after 2 weeks of ribavirin which was negative. At the time of discharge patient was asymptomatic and hemodynamically stable. He did not have any respiratory or neurological complications of nipah infection but his secretions were positive for viral PCR. Even then he was started on high dose ribavirin on day 1 of fever and was continued for 14 days until a repeat viral PCR became negative.

Case 7

19 year old female presented to the casualty with fever, cough, headache, vomiting, altered sensorium and breathlessness for 6 days duration. She had a history of contact with index Nipah case on 5/5/2018. On examination, patient was drowsy, febrile with tachypnea and tachycardia. Respiratory system examination revealed t b/l crepitations. She had no focal neurological deficits. At the time of admission her investigations revealed normal complete blood count except for mild thrombocytopenia. Her renal and liver function tests were normal. A possibility of nipah infection was suspected in view of the altered sensorium and possible contact with index case. A lumbar puncture done was normal except for high opening pressure. Chest x ray showed multiple alveolar infiltrates and ct thorax was suggestive of ARDS. Her viral PCR for nipah infection came as positive. She was given non invasive ventilation, antiviral drug ribavirin 1000mg q6H for 14 days and other supportive measures. She slowly improved and finally on 5th day of illness she was conscious oriented. Her viral PCR was repeated after 14 days which became negative and she was discharged 21 days later fully conscious oriented with no sequelae.

Case 8

32 year old female, housewife from Thirurangadi, Malapuram was admitted with fever and chills, myalgia, nausea, vomiting, loose

stools, lower abdominal pain of 3 days duration. It was associated with altered behaviour of one day duration. There was no history of headache or seizure. She then developed cough with blood tinged expectoration and breathing difficulty and was brought to casualty. On examination patient was conscious oriented, tachypneic with an oxygen saturation of 70% with high flow oxygen. There were bilateral crepitations in chest and no focal neurological deficits or neck stiffness. Investigations showed total count on lower side, but there was no thrombocytopenia and other blood parameters were within normal limits. Chest x-ray showed bilateral infiltrates s/o severe ARDS. Dengue serology was negative. In view of tachypnoea and saturation fall patient was intubated and mechanical ventilation started and other supportive measures given.

Next day of admission patient went in to hypotension, managed with IV fluids and inotropes. ECHO showed global LV hypokinesia. In spite of supportive measures patient expired on 3rd day of admission. Samples sent for virology become positive for NIPAH virus

So the final diagnosis was viral encephalitis with severe ARDS, myocarditis due to NIPAH virus

Case 9

75 yr. old female was admitted with deliberate self harm with ingestion of about 30 tablets of amlodipine following which she developed tiredness sweating and vomiting. She was given stomach wash in nearby hospital and when she became drowsy and breathless and was shifted to govt medical college Calicut MICU. At MCH She was ventilated, given supportive care and was treated as acute pulmonary odema and metabolic encephalopathy following toxic dose of amlodipine. She improved and was shifted to ward 3 days later. On the second day after transfer to ward she developed fever with altered sensorium. The next day she developed severe respiratory distress and chest examination revealed bilateral crackles. Her antibiotics were changed, all supportive care was continued. Her metabolic parameters at this time was normal and her sudden development of altered sensorium and respiratory difficulty made us think of the possibility of her acquiring of

nipah infection from ICU were some of the cases had died at that time with clinical features similar to nipah. Hence she was isolated, started on high dose ribavirin along with all other conservative measures and samples were sent for nipah serology. She succumbed to illness on next day and her results of nipah serology came as positive on the day of her death.

Case 10

The last patient of the series was a 25 year male manual labourer, apparently normal person got admitted in Taluk hospital Balussery 2 weeks back for Abdominal pain, fever, diffuse abdominal pain with watery loose stools with blood and mucus in stools. He was managed as acute dysentery with intravenous antibiotics, Ceftriaxone for 4 days and got discharged on oral antibiotics. He took total 7 days of antibiotics and symptomatically improved. Fever subsided, frequency of stools became normal.

Few days later he started having fever, abdominal pain and watery loose stools. Fever was low grade with abdominal pain. He was again managed with IV antibiotics. But symptoms didn't improve hence referred here. On taking detailed history, he had contact with proven case of Nipah disease. Hence he was sent to isolation ward for virology study. Fever was low grade with diffuse bifrontal headache and neck pain. There were no focal deficits, vomiting/ seizures. He had large volume watery stools with no blood/mucus in stools. He was started on IV ceftriaxone, and other symptomatic measures. Nipah virology was sent, and the report came as negative. Hence he was shifted to medicine ward.

The next day of his shift to ward he developed irrelevant talk. He was not answering to questions. He then became drowsy. The same day he developed bilateral ptosis, but his ocular movements were full in all directions eye movements full. No other cranial nerve symptoms. He also showed autonomic dysfunction in the form of profuse sweating and fluctuating blood pressure. He did not have any respiratory symptoms but his saturation started falling by evening. He was maintained on high flow oxygen. His respiratory system examination revealed bilateral crackles later. ABG was s/o ARDS. In view of contact

history, neurological and respiratory symptoms, we still suspected nipah virus infection and he was transferred back to isolation ward ICU, nipah virology samples sent again. He was intubated as general condition was worsening. In spite of all measures he expired and his repeat virology study comes as PCR positive for nipah virus.

Discussion

These were 10 of the probable as well as suspected cases of nipah admitted in government medical college Calicut when the first nipah outbreak occurred in May 2018. Patients with suspected cases of Nipah virus infection were persons residing in the outbreak areas or who had contact with positive cases who experienced fever with either headache or altered mental status during the time of the outbreak.³ Almost all the patients of this series had similar clinical picture starting with fever and succumbing to illness within 5-6 days with neurological and or respiratory complications. The four suspected deaths occurred before the official declaration of Nipah epidemic was made hence they received the conservative treatment only. Out of the six positive patients four received high dose Ribavarin of which 2 survived. The patients were mainly in 3 hospitals the Perambra govt hospital, Baby Memorial hospital and Govt Medical college, Calicut.

The first patient who was admitted with fever altered sensorium and diarrhoea was initially admitted in Perambra Government. It was from there that he was shifted to government medical college Calicut on 5th of May 2018 and he died on the same day with a diagnosis of viral encephalitis and ARDS. Subsequently 10 days later 2 members from his family developed similar symptoms and succumbed to the illness and it was in them that the deadly nipah infection was confirmed. So probably case 1 would have been the index case from whom all others contracted the deadly virus. His main symptoms were fever, vomiting altered sensorium and diarrhoea. Diarrhoea has not been described in the previous outbreaks in Bangladesh but was seen in 26% of cases in Singapore outbreak.⁴ How the index case got the infection is a subject of discussion. The veterinary experts have identified nipah virus in fruit bats at Perambra. Probably the

index case got infection from eating fruits contaminated by secretions from bats. Bats are abundant in Perambra village and so are mangroves.

The second case initially was admitted in Perambra hospital when the index case was also there. He probably contracted the infection from the index case. The recurrent fever 5 days after his admission was probably the beginning of nipah infection. He soon worsened and developed symptoms of encephalitis ad ARDS similar to the first patient and succumbed to the illness. He died before the nipah epidemic was confirmed and hence his samples were also not sent for virological analysis.

The third case was a hospital staff of govt Medical College Kozhikode. She probably contracted the infection from index case on 5th of May when the index case was admitted here. She had predominant respiratory involvement in the form of cough breathlessness which progressed to ARDS. She had also developed myocarditis in the form of hypotension, elevated troponin 1 and left ventricular dysfunction on echo. Case 1, case4, case 5 and case 7 had also features of myocarditis. The cardiac involvement has not been described in the previous nipah outbreaks. A more detailed analysis of the cardiac manifestations of Nipah infection will have to be undertaken.

Case 6 and case 7 are the only survivors of this epidemic. Case 6 was a male patient whose wife had died of nipah infection. He was isolated on the first day of fever and also was started on high dose ribavarin. He did not develop any of the cardiac or neurological complications and his fever subsided after 7 days.

Case 7 also did contract the illness from casualty on 5th of May. She had developed encephalitis as well as ARDS. She was started on high dose Ribavarin and she improved and recovered completely without any sequel.

Case 10 was the last case in the series. He was initially negative for Nipah and later when he developed prominent clinical symptoms his samples were repeated and it turned out to be positive. His initial symptom of diarrhoea for which he consulted a local doctor could have been due to some other bacterial infection. It was from the local hospital did he have contact

with a probable nipah case. Since he had had contact with a positive patient he was initially isolated. But his initial blood urine and throat swabs were negative for viral PCR. His symptoms continued. His diarrhoea persisted and he started developing neurological symptoms in the form of bilateral ptosis and ataxia. In the Malaysian outbreak the brainstem dysfunction in the form of segmental myoclonus, areflexia and hypotonia, hypertension, and tachycardia were seen in 55% of the patients.⁴ Here our patient had bilateral ptosis which could also be due to brainstem involvement. The case 7 had also abnormal movements of one upper limb which could not be classified as seizure. This could be due to involvement of extrapyramidal system.

The investigations mainly revealed a viral picture with leucopenia and thrombocytopenia. As all patients were previously healthy the renal and liver function tests were normal in all patients. The lumbar puncture was not done in all patients but in those patients it was done revealed a high pressure with no cells.

Thus we find that these patients had predominant respiratory and neurological symptoms along with gastrointestinal manifestations. The striking feature is the cardiac involvement which was not seen in previous outbreaks. The symptomatology of these patients in the present Kerala outbreak are more similar to Bangladesh outbreak.⁵ Malaysian outbreak did not have much of respiratory symptoms.⁵ Also human to human spread is maximum in our outbreak and it is a point source epidemic as all positive cases were primary or secondary contacts of the index case.⁴ The more incidence of human to human transmission is probably due to increased incidence of respiratory symptoms as well as diarrhoea. The genetic makeup of the nipah virus is different in both Bangladesh and Malaysian outbreak and that is probably responsible for the different manifestations.⁵ The present Kozhikode outbreak is produced by a viral strain which is probably similar to Bangladesh strain. Since we could identify the virus in the second case itself we could contain the infection without an alarming increase in the number of casualties. Initially we

did not have strict infection control practices but once the virus was isolated we followed strict barrier nursing, isolated the patients wore full personal protection equipments and did proper waste disposal and hence could control the infection without much casualties.

Summary

Nipah virus is an emerging zoonotic illness which is deadly virus with a very high mortality rate of 70-90%. Symptoms includes: fever and headache within three-14 days of exposure an incubation period of five to 14 days.⁶ The clinical signs are fever, headache, and vomiting, followed by drowsiness, disorientation and mental confusion as well as cough, and breathlessness. Brainstem dysfunction in the form of autonomic disturbances and cranial nerve involvement is a notable clinical feature.⁷ The origin of infection is likely to be intake of food contaminated by fruit bats. The cardiac manifestations have not been described in the previous

outbreaks of nipah infection. Infection control practices and proper barrier nursing helped to control the infection at the earliest.

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