CASE SERIES

Dengue fever presenting as acute febrile illness in neonates: A case series from Pakistant

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Abstract

Dengue fever is a mosquito-borne disease caused by flavivirus. It primarily infects people living in tropical and subtropical areas and can be transmitted vertically or horizontally to new-borns. We discuss the clinical spectrum, treatment, and outcomes of five neonates who presented with dengue fever at Aga Khan Hospital for Women in Karimabad, Karachi, Pakistan, during the 2021 post-monsoon season (October to December). Dengue infection was confirmed via positive NS1 antigen test. All new-borns had fever, flushing, and thrombocytopenia. Capillary leak syndrome and haemorrhagic complications occurred in one case. Two babies required oxygen support, with one mortality. Due to the severity of the disease in this population, we suggest that dengue fever should be evaluated as a differential diagnosis in neonates with sepsis and thrombocytopenia, especially in high-risk or endemic areas. Critical management strategies for neonatal dengue fever are the same as those for other paediatric patients and include judicious use of intravenous fluids and inotropes.

Keywords: Neonate, dengue fever, thrombocytopenia, dengue haemorrhagic fever, dengue shock syndrome.

DOI: https://doi.org/10.47391/JPMA.8260

Submission completion date: 15-11-2022
Acceptance date: 27-05-2023

Introduction

Dengue fever is one of the most common mosquito-borne illnesses. The rapid increase in infection rates possibly due to climate change, has caused substantial health problems.[1] Inadequate public health awareness, sanitation, hygiene, and poor socioeconomic conditions further exacerbate the severity and complications of dengue fever.[2] Despite reported cases of neonatal dengue, literature on its various manifestations and outcomes in this population is scant. This case series aims to fill this gap by describing clinical presentations and outcomes in five neonates who tested positive for dengue fever.

Dengue virus is an arthropod-borne pathogen spread to humans by the bite of a flavivirus-infected female mosquito, primarily *Aedes aegypti*. The Flaviviridae family of viruses that causes dengue has four serotypes, DEN1, DEN2, DEN3, and DEN4, all of which can infect humans. Virtually no cross-protection has been observed, implying that immunity is serotype-specific. Incubation lasts between three to 14 days.[3] Clinical manifestations range from asymptomatic infection, mild flu-like illness, and sometimes fatal bleeding.[4] Dengue fever can also present differently in different age groups. For example, fever and vasomotor symptoms (e.g., blotching and mottling) are the most prominent clinical manifestations in the neonatal age group, followed by hepatomegaly and fever. Rash, hepatomegaly, fever, and petechiae are commonly seen in older infants. Fever, rash, arthralgia, and myalgia are common symptoms associated with dengue-related thrombocytopenia, leucopoenia, and hepatomegaly in older children.[1,5] Transmission in neonates can be acquired vertically from the mother or horizontally in the postnatal period. Vertical or congenital dengue should be suspected in neonates born to mothers with dengue fever within 10 days before to 10 hours after delivery. The affected neonate can manifest symptoms up to 11 days after birth.[6] Although vertical transmission is not commonly reported, prevalence rates among pregnant women and neonates have increased due to the current endemic situation in Pakistan. A study conducted in India in 2020 reported a 1.6% rate of vertical transmission of dengue.[6]

Case Series

Case 1: An 18-day-old, full-term baby boy weighing 3.1 kg was admitted with fever and lethargy for about one day in October 2021. Maternal history was non-contributory. An examination revealed mottled skin and fair neonatal reflexes with a heart rate of 160 beats/minute and respiratory rate of 48 breaths/minute. His peripheral capillary refill rate was 3 seconds, the liver was non-palpable, and no visible rashes or petechiae were observed. The baby was admitted with presumptive diagnosis of sepsis. Parenteral antibiotics were administered. Initial lab investigation showed haemoglobin of 16.2 g/dl, haematocrit of 48.2, total leukocyte count of 7.2×10^9/L, platelet count of 419×10^9/L, normal serum c-reactive protein, and detailed urine report (colour yellow, appearance clear, pH 5, specific gravity 1.017, no casts, no

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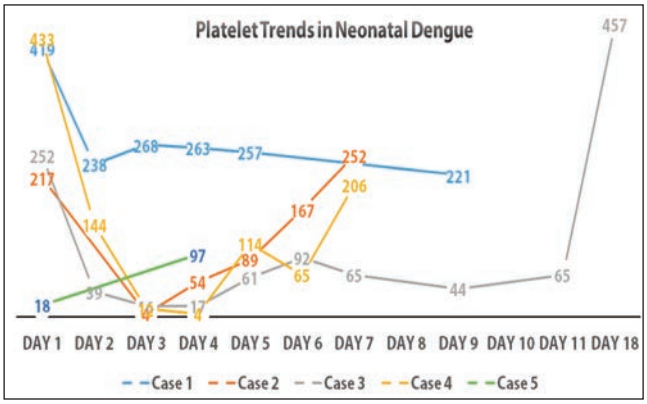

Figure-1: Platelet count trends in five cases of neonatal dengue fever.

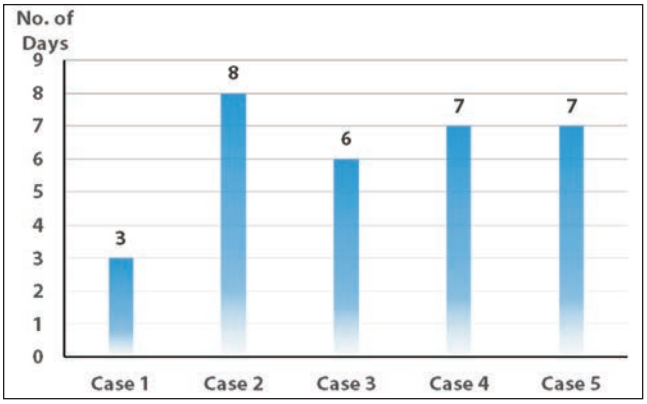

Figure-2: Fever duration (days) in five cases of neonatal dengue fever.

red blood cells, negative for nitrite, and leucocyte esterase). Considering the clinical presentation along with the sudden drop in platelets with no identification of focus, dengue was considered as a differential (Figure 1). The infant's NS1 antigen report was positive within 48 hours of fever. Antibiotics were discontinued after confirming no growth on blood culture. Supportive treatment with IV fluids and paracetamol was continued. Serial platelet, haemoglobin, and haematocrit monitoring were done, which remained within normal ranges. The total duration of fever was three days (Figure 2). The baby remained stable and was discharged home after three uneventful days of admission (Table)

Case 2: A 27-day-old (weight 2.9 kg), baby girl born at 36 weeks presented with fever and lethargy for about one day in October 2021. There was no history of rash, bleeding, or feed intolerance. On examination, the baby was febrile, with generalised mottling and poor neonatal reflexes, heart rate of 170 beats/minute, and respiratory rate of 45 breaths/minute. She was admitted and started on treatment for possible neonatal septicaemia. Parenteral fluids and antibiotics were initiated. The initial workup showed haemoglobin of 17.0 g/dl, haematocrit of 51.7, total leukocyte count of 5.6×10^9/L, platelet count of

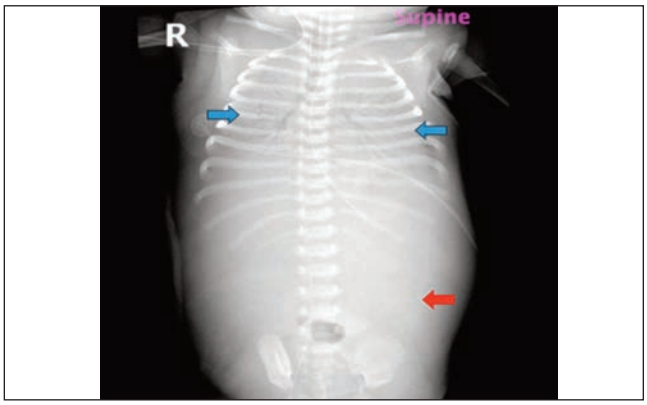

Figure-3: X-ray image of the chest and abdomen showing complete opacification of both lung fields, suggesting pulmonary haemorrhage (blue arrows). Paucity of air in the bowel loops is noted with generalised haze of the abdomen, due to ascites (red arrow).

217×10^9/L, and elevated C reactive protein. A complete blood count repeated after 24 hours showed significantly worsening thrombocytopenia at 5×10^9/L (Figure 1). Similar to case 1, the clinical presentation and sudden drop in platelet count led to suspicion of dengue fever. The NS1 antigen test was positive. The baby was transfused with irradiated platelets. Supportive treatment was continued, and a repeated blood count showed increasing platelets. No bleeding, capillary leak syndrome, or haemodynamic instability was observed during admission. Radiological investigations for intracranial bleeding, ascites, and pleural effusion were unremarkable. The baby remained febrile for seven days with persistent mottling and lethargy (Figure 2). On the sixth day of admission, the baby was discharged in stable condition (Table)

Case 3: In November 2021, a six-day-old, full-term, baby girl weighing 3 kg was admitted with fever and yellowish discolouration of the skin since the last two days. There was no history of rashes, convulsions, bleeding, diarrhoea, or feed intolerance. The mother had experienced acute febrile illness associated with severe body aches, arthralgia, and myalgia two days before delivery. On investigation, the mother's NS1 antigen test was positive. The baby was born via spontaneous vaginal delivery and remained well until fever developed on the sixth day of life. On examination, the baby was febrile, deeply icteric up to her feet, lethargic, and had poorly responsive neonatal reflexes. Her heart rate was 160 beats/minute and respiratory rate was 49 breaths/minute. Initial lab investigations reported hyperbilirubinaemia of 28.8mg/dl, haemoglobin of 19 g/dl, haematocrit of 63.2, total leukocyte count of 7.3×10^9/L, and platelet count of 252×10^9/L. The baby was admitted and treated for possible sepsis and neonatal jaundice. Intensive phototherapy was started along with intravenous fluids and antibiotics. A repeat serum bilirubin level within four hours of phototherapy measured 20 mg/dl, and jaundice

was managed accordingly. The baby continued to have fever spikes, which were treated via intravenous paracetamol. On her second day of admission, she developed generalised mottling and petechiae on her face which spread to her abdomen. Her abdomen was tense and distended with inaudible gut sounds, and her platelet count dropped from 252×10^9/L to 39×10^9/L within 24 hours of admission (Figure 1). An NS1 antigen test was done which came positive. Irradiated platelets were transfused. Radiological investigations revealed mild ascites and pleural effusion with no evidence of intraventricular haemorrhage. The baby was kept nil per oral with oxygen support via nasal prongs. Hypoalbuminaemia of 3 gm/dl was reported. Her post-transfusion platelet count dropped again from 85×10^9/L to 16×10^9/L within the next 24 hours and was managed with repeat platelet transfusion. On the fourth day, her condition improved and the fever resolved (Figure 2). Antibiotics were discontinued as blood and urine cultures were inconclusive. Oral feeding was resumed. Serial platelet,

Table: Summary of cases of neonatal dengue fever.

	Case 1	**Case 2**	**Case 3**	**Case 4**	**Case 5**
General					
Age of Presentation (days)	18	27	6	23	35
Gender	Male	Female	Female	Female	Male
Maternal history	-	-	+	-	+
Birth weight (kg)	3.1	2.9	3	3	2.9
Symptoms					
Fever	+	+	+	+	+
Fever duration	3	8	6	7	7
Lethargy	+	+	+	+	-
Signs					
Neonatal reflexes	Normal	Poor	Poor	Poor	Poor
Petechiae/rash	-	-	+	+ (day 3)	-
Jaundice	-	-	+	-	-
Flushing	+	+	+	+	+
Bleeding	-	-	-	+	+
Mottled skin	+	+	+	+ (day 3)	-
Abdominal distension	-	-	+	+ (day 3)	-
Delayed capillary refill	+	+	+	+ (day 3)	-
Heart rate	N	Increased	N	Increased	N
Respiratory rate	N	N	N	N	N
Investigations					
Haemoglobin (g/dl) (Normal range – 15-21 g/dl)	16.2	17	19	14	8.4
Haematocrit (Normal – 45 – 67)	48.2	51.7	63.2	43.4	26.3
Platelet (109/L) (on admission) (Normal range – 210-500 x 10^9/L)	419	217	252	433	18
Platelet (109/L) drop within 24 hours (Normal range – 210-500 x 10^9/L)	238	4	39	144	-
Hypoalbuminaemia	-	-	+	+	-
Dengue NS1 antigen	+	+	+	+	+
Radiological findings of third spacing	-	N	Pleural effusion + Ascites	Pleural effusion + Ascites	-
Diagnosis	Dengue Fever	Dengue Fever	Dengue Haemorrhagic Fever	Dengue Shock Syndrome	Dengue Fever
Management	IV fluids IV Paracetamol	IV fluids IV Paracetamol Platelet Transfusion	IV fluids Paracetamol Platelet Transfusion (twice)	IV fluids IV Paracetamol Platelet Transfusion Inotropes Invasive ventilation	Oral Paracetamol
Outcome					
Complication	-	-	Pleural effusion Ascites	Hematemesis Respiratory Distress Pleural effusion Ascites Pulmonary haemorrhage	-
Condition on discharge	Stable	Stable	Stable	Expired	Stable
Duration of stay (days)	3	6	12	6	Treated as outpatient

+ Present, - Absent, N Normal

haemoglobin, and haematocrit levels also improved. The baby was discharged in stable condition after 12 days of admission. (Table)

Case 4: A 23-day old baby girl, born at 37 weeks' gestation, weighing 3 kg, was admitted with a fever lasting one day in November 2021. There was no history of convulsions, rashes, or bleeding. The mother's past medical history was unremarkable. On examination, the baby was febrile with mottled skin, fair neonatal reflexes, heart rate of 158 beats/minute, and respiratory rate of 55 breaths/minute. Initial lab investigations revealed haemoglobin level of 14.2g/dl, haematocrit of 43.4, total leukocyte count of 5.8×10^9/L, platelet count of 433×10^9/L; C reactive protein and urine analysis were within normal ranges. The baby was admitted with presumptive diagnosis of neonatal septicaemia. Parenteral antibiotics were started. Oral feeding was continued. The baby had persistent spikes of fever ranging between 100 to 102°F. The NS1 antigen test was positive. Her repeat platelet count dropped to 144×10^9/L within 24 hours (Figure 1). On the third day of admission, the baby's clinical condition deteriorated with diffuse petechial rash, vomiting, and abdominal distention with discoloration of the abdominal wall. Platelets declined from 144×10^9/L to 30×10^9/L in the next 24 hours. The baby was kept nil per os with intravenous fluids. Platelets were transfused. Pleural effusion and moderate ascites were observed on chest X-ray and ultrasound of the abdomen (Figure 3). Within the next 48 hours, her condition deteriorated further with haematemesis, pulmonary haemorrhage, hypoalbuminaemia, and hypotension. The baby was intubated, transfused with blood products, and given inotropic support. Despite aggressive management, her condition deteriorated, and the baby expired on the seventh day of admission. (Table)

Case 5: In November 2021, a 35-day old baby boy, born at 36 weeks' gestation with a weight of 2.9 kg, was brought to the clinic with a fever lasting three days and one episode of epistaxis. The baby was febrile and flushed with no signs of anaemic failure or hypoperfusion on examination. Maternal history was positive for fever lasting two days till a week before admission. Initial lab investigations revealed haemoglobin level of 8.4 g/dl, haematocrit of 26.3, total leukocyte count of 8.3×10^9/L, and platelet count of 18×10^9/L (Figure 1). Admission was advised for further management, but the patient's family refused. The baby was discharged against medical advice with intravenous antibiotics and oral paracetamol and instructed to return for a repeat platelet count the next day but returned after three days, for follow-up. Despite late follow-up, the infant was in a stable condition. with resolution of fever and epistaxis. The NS1 antigen test was positive, and blood and urine cultures were inconclusive. Another platelet count repeated on day four of discharge confirmed an improving trend. The baby's fever lasted seven days (Figure 2), but no platelet transfusion was needed. (Table).

Discussion

While dengue fever in the paediatric and adult populations is well-documented, little is known about its clinical manifestations in the neonatal age group, most likely due to under diagnosis or misdiagnosis as neonatal septicaemia. Moreover, few studies have examined the horizontal transmission of neonatal dengue fever.[7,8] Due to the high prevalence and infectivity rate, dengue fever has become a challenge for the public health sector, especially in low-income countries.

In our case series of five neonates with dengue fever, all the patients presented with acute febrile illness, mottling, flushing, and thrombocytopenia. It is thus recommended that all infants presenting as such, particularly during the dengue epidemic season, should be evaluated for dengue fever. The symptoms observed in the above-mentioned neonates are similar to those for older children, though a flushed appearance was more evident upon examination of the neonates, whereas petechiae and epistaxis are more frequently observed in older children. Management did not differ between both age groups.

In this case series, four out of five cases exhibited horizontal transmission because all mothers were asymptomatic during childbirth and for 10 days after, though no dengue serology tests for the mothers was conducted. The four neonates who acquired dengue horizontally presented on different days of life, with a mean age of 25.75±9.11 days. Similar findings have been reported in India, with ages ranging from 24 to 26 days.[9,10] Only one infant (case 3) exhibited vertical transmission of the virus, with symptoms starting around the sixth day of life. In India and Vietnam, the mean age of neonates with vertical transmission of dengue is reportedly 11.25 days and 7 days, respectively.[1,9]

Fever was the most common symptom and flushing the most common sign in all five neonates, which echoes findings in the literature.[11] Mottling, which indicates vasomotor instability, was present in two neonates on arrival and two during their hospital stays. Most literature does not support gender differences regarding neonatal dengue; three of our five cases were females. All patients were diagnosed in the dengue epidemic season in Pakistan.[9] WHO defines dengue haemorrhagic fever as the presence of fever, thrombocytopenia, haemorrhagic tendency with evidence of plasma leakage, and haemoconcentration ≥20% above average for age, sex, and population, and signs include plasma leakage such as

pleural effusion, ascites, and hypoproteinaemia. Dengue shock syndrome is characterised by evidence of circulatory failure.[5] In the current case series of five infants, three were classified as having dengue fever, and two developed complications and were classified as having dengue haemorrhagic fever and dengue shock syndrome.

Dengue antigen testing was considered due to availability of the test. Rapid early decline in platelet count (more than $2x10^9$ within the first 24 hours) during the acute febrile phase was noted in four out of five cases. Leukopenia was not observed, and haematocrit levels remained within normal ranges in all five infants, including the cases of dengue haemorrhagic shock.[9,12] Radiological investigations revealed pleural effusion and ascites in both the cases of dengue haemorrhagic fever with dengue shock syndrome.

Three cases required platelet transfusion. Three patients were discharged in stable condition. One neonate with dengue shock syndrome required intubation and inotropic support and expired on day six of admission. The mean hospital stay was 6.75±2.16 (4–10) days.[9,13]

Conclusion

Dengue fever should be considered in all neonates and pregnant women presenting with acute febrile illness with thrombocytopenia, especially in mosquito-prevalent tropical areas and in the monsoon season. The clinical presentation and management strategies for neonates in this case series generally follow the same guidelines as those for paediatric patients, according to WHO.

Disclaimer: No case presented herein is individually identifiable. Verbal consent was taken from parents during the hospital stay and interaction.

Conflict of interest: None.

Funding disclosure: None.

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