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Dengue fever in a 32-day-old patient. A rare case report

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ABSTRACT

Dengue fever is a viral disease transmitted by the *Aedes aegypti* mosquitoes.

In Argentina, dengue fever is an epidemic disease; most cases are reported during the hot months. Until epidemiological week (EW) 20/2023, 106 672 cases were reported across 18 of the 24 provinces of Argentina. Children younger than 2 years are among the main groups at risk. Recognizing signs and symptoms and identifying risk factors is fundamental for the management of cases at a higher risk of severity.

Here we describe the case of a 32-day-old female patient who was hospitalized due to febrile syndrome without a source, who had a differential diagnosis of viral meningitis and sepsis and progressed to leukocytosis, thrombocytopenia, hypoalbuminemia in association with rash and edema. The diagnosis of dengue fever was established based on clinical, epidemiological, and positive IgM data.

Keywords: *dengue; fever of unknown origin; sepsis; viral meningitis; dengue vaccine.*

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INTRODUCTION

Dengue fever is caused by an arbovirus RNA of the *Flaviviridae* family, with 4 serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) distributed across the Americas. Dengue fever is a systemic and dynamic infectious disease with a broad spectrum of manifestations.[1] The risk of severe dengue is associated with different factors, including age younger than 2 years and infection with a serotype followed by infection with a different serotype. According to a report by the Pan American Health Organization (PAHO), the number of cases and deaths due to dengue fever increased in 2022. The 4 countries with the greatest incidence were Bolivia (552.78 cases/100 000 inhabitants), Nicaragua (260.30 cases/100 000 inhabitants), Belize (145.58 cases/100 000 inhabitants), and Brazil (166.8 cases/100 000 inhabitants).[2]

In Argentina, dengue fever is an epidemic disease; most cases are reported during the hot months (November through May).[2]

Until epidemiological week (EW) 20/2023, 106 672 cases were reported in our country. The following jurisdictions confirmed endemic circulation of dengue fever: Central region (Buenos Aires, the City of Buenos Aires, Córdoba, Entre Ríos, and Santa Fe); Northwest region (Catamarca, Jujuy, La Rioja, Salta, Santiago del Estero, and Tucumán); Northeast region (Chaco, Corrientes, and Formosa), except for Misiones; San Luis and Mendoza in the Cuyo region; and La Pampa in the South region. Reported dengue serotypes depend on the epidemiological moment; between 2022 and 2023, DENV-2 (81.16%), DENV-1 (18.79%), and DENV-3 (0.05%) prevailed in Argentina.[3] Here we describe the case of a 32-day-old female patient who was admitted due to fever without a source who developed signs consistent with dengue fever over the hours.

CASE REPORT

A 32-day-old female infant, with no relevant perinatal history, consulted due to fever for the past 12 hours. She was admitted with suspected sepsis for diagnosis and treatment. Her father was experiencing upper airway disease, but no history of travel, sick relatives or neighbors was reported. The family lived in Moreno, in the province of Buenos Aires.

Two blood cultures, a urine culture, and a cerebrospinal fluid (CSF) culture were performed. No CSF polymerase chain reaction (PCR) was done to look for enterovirus or herpes virus.

The patient's cytochemical panel was positive, so her condition was deemed as viral meningitis and an empirical antibiotic therapy with ampicillin and ceftriaxone was started. Her antigen test and COVID-19 PCR were negative. Her urine test was normal. Her virological test of nasopharyngeal secretions was negative. Lab test results are shown in *Table 1*.

On day 2, she had fever, tachycardia with distal peripheral cyanosis, and generalized reticulation and required supplemental oxygen and volume expansion with intravenous fluids, with an adequate response. Due to suspected sepsis, new lab tests and 2 blood cultures were done. The antibiotic therapy continued.

Abdominal distension was observed on day 3. The oral route was interrupted and fluid intake and output were controlled. The abdominal ultrasound showed hepatomegaly; perivesicular fluid; splenomegaly; and free fluid around the liver, among the loops, and in the pelvis. The pleural ultrasound showed mild right pleural effusion. The patient's leukocyte count increased and thrombocytopenia and hematocrit values decreased from admission, which was deemed as secondary to the management of the internal milieu in a severe patient with fluid extravasation. Dengue fever was suspected, so a serology test was performed, which showed a positive IgM and a negative NS1 antigen.

On day 4, the patient developed a generalized, confluent macular erythematous rash that left parts of healthy interposed skin in islets with no pruritus. She developed leukocytosis, which was deemed as an inflammatory response, and thrombocytopenia. Her cultures were negative. The patient was referred for consultation to the Department of Infectious Diseases and Hematology. The antibiotic therapy was discontinued. The probable diagnosis was assumed to be dengue fever (*Figure 1*).

On day 5, she developed generalized edema with negative Godet's sign. She began testing for tolerance to oral feeding.

On day 6, she had no fever, her edema had resolved, she had a good attitude and oral tolerance, and her rash had reduced. A large increase in leukocyte count, a rising platelet count, and an improved albumin level were observed.

On day 7, the patient did not have any edema. Her white blood cell count was going down. The serology test for dengue fever was repeated

Table 1. Progress of most relevant lab tests

Test	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Hct (%)	43	37.4	31	33.9	34.4	30	29
Hb (g/dL)	14.7	13	11.7	12	12	11	10.7
WBC (cells/mm^3)	8590	10 100	17 700	22 400	55 700	76 400	46 800
N/L/M (%)	46/32.1/11.5	57/25/8	61/24/5	43/28/18	18/60/9	5/75/13	9/76/7
PLT (cells/mm^3)	301 000	139 000	97 000	115 000	119 000	134 000	194 000
U/C	16/0.4				10/0.17	3/021	
Albumin (g/dL)					2.6	3.1	
PRO (ng/mL)	0.28						
PCR (mg/dL)		42.6	65				
Na/K/Cl (mEq/L)		129/4/95				136/4/104	
CSF	Colorless, slightly xanthochromic						
PROT (mg/dL)	66						
GLU (mg/dL)	59						
GLU (mg/dL)	91						
LEU	110/mm^3						
MO	80%						
Dengue fever							R
IgM			Positive				
NS1 antigen			Negative				NR
Viral genome			UND				

Hct: hematocrit. Hb: hemoglobin. WBC: white blood cells. N/L/M: neutrophils/lymphocytes/monocytes. PLT: platelets. U/C: urea/creatinine. PCR: polymerase chain reaction. NA/K/Cl: sodium/potassium/chloride. PRO: procalcitonin (normal range: 0.5–2.4).
Serology for dengue IgM, sample 1 collected on day 3: MAC-ELISA technique to detect IgM, and sample 2 collected on day 7: commercial ELISA technique to detect IgM.
NS1 antigen, sample 1 collected on day 3: immunochromatography technique; NS1 antigen, sample 2 collected on day 7: ELISA technique to detect NS1.
NR: non-reactive. R: reactive.
Viral genome: RT-qPCR technique.
UND: undetectable
CSF: cerebrospinal fluid. PROT: CSF protein level. GLU: CSF glucose level. LEU: leukocytes. MO: mononuclear. Glu: blood glucose level.

and showed positive IgM. The diagnosis was confirmed. It was not possible to establish the serotype.

On day 9, the patient was discharged.

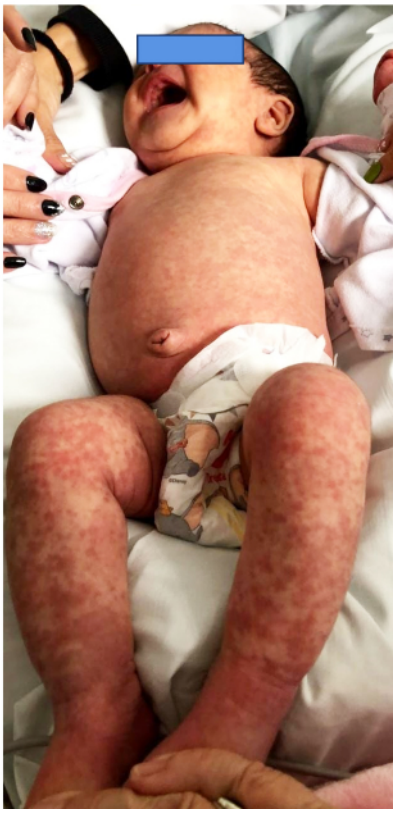
DISCUSSION

Dengue fever is a growing global public health problem due to climate change, population growth in urban areas, insufficient water supply, inadequate waste collection, containers that serve as mosquito breeding sites, increased travel and migration, and failures in vector control.[4]

Dengue fever is a notifiable disease. Prevention is based on immunization and vector control, with proper disposal of solid waste and improved water storage practices to prevent female mosquitoes from laying eggs.[5]

In April 2023, the National Drug, Food and Technology Administration of Argentina (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, ANMAT) approved the use of a dengue vaccine developed by Japanese pharmaceutical company Takeda, for individuals aged 4 years and older, whether or not they suffered from dengue fever before. The vaccine is called TAK-003.[6] However, no vaccine can block an outbreak of dengue fever. For all age groups, the best prevention strategy is still the control and elimination of mosquito breeding sites, the avoidance of mosquito bites, and the use of vector isolation methods (repellents, mosquito coils, mosquito nets, etc.).[7,8] In endemic areas, it is important to keep in mind the possibility of mother-to-child transmission, mainly in babies

Figure 1. Physical examination on day 4



Generalized, confluent macular erythematous rash that leaves parts of healthy interposed skin with clear islets in between. Edema in both lower extremities.

born to mothers with peripartum febrile symptoms, rash, hepatomegaly, and thrombocytopenia, with or without clinical signs of sepsis during the first 2 weeks of life.[2]

Dengue is a self-limited febrile disease with an incubation period of 4 to 10 days. The febrile phase of 2 to 7 days marks the onset of the sudden onset disease that usually remits on the third day with leukopenia, mild thrombocytopenia, and a moderate increase in transaminases.

In children, the early signs and symptoms of the disease are non-specific and undifferentiated from other acute febrile illnesses.[9] Dengue fever with warning signs is characterized by 1 or more of the following: severe and sustained abdominal pain, persistent vomiting, serous effusion, mucosal bleeding, change in mental status, hepatomegaly, increased hematocrit level, decreased platelet count. Severe dengue is characterized by 1 or more of the following: severe plasma extravasation, expressed by hypovolemic shock or respiratory distress due to excess fluid in the lung; severe bleeding; severe hepatitis (transaminases above 1000 units); encephalitis; myocarditis.[10–12]

Rash first develops on day 3–4. The critical phase starts between day 3 and 7. Increased hematocrit level, hypoalbuminemia, perivesicular effusion, pleural effusion, ascites, and generalized edema may be observed. Such capillary leakage may cause dengue shock syndrome. The recovery phase lasts 2 to 3 days, with a rapid recovery of thrombocytopenia. The alteration of vascular permeability lasts 48–72 hours, with a rapid clinical improvement.[9]

Thrombocytopenia (68.46%) is the most frequent finding. Enzyme-linked immunosorbent assay (ELISA) and reverse transcriptase polymerase chain reaction (RT-PCR) are the main laboratory diagnostic modalities to detect nonstructural protein 1 (NS1) antigen, IgG, and IgM in the late phases.[13] The detection of viral antigens (NS1 Ag) (viremia) is the method of choice in the first 5 days of disease; whereas serological tests are used as of day 5–6.

Leukocytosis may be observed, as in our

patient,[14] and an increased hematocrit level is a sign of hemoconcentration secondary to fluid transfer and hypovolemia. The World Health Organization considers a variation equal to or greater than 20% in the hematocrit level, either an increase from baseline or a decrease during the convalescent phase from the critical phase, to be diagnostic of dehydration. But such changes are not observed if hypovolemia is managed in an early manner.[15] In our patient, a progressive decrease was observed. She was offered early supportive treatment with adequate hydration, especially after the resolution of fever.[9]

Other recommendations include rest, not using aspirin or NSAIDs, using repellents, and implementing environmental control measures to prevent mosquito bites during the febrile phase and to prevent transmission at the hospital or at home.[2]

The final diagnosis in our 32-day-old patient was severe dengue. The differential diagnoses included viral meningitis, sepsis, and dengue shock syndrome. The early identification of signs and symptoms serves as a window of opportunity for effective treatment. ■

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