

## ACUTE RHABDOMYOLYSIS IN A JUVENILE WITH DENGUE FEVER: A RARE MANIFESTATION BUT BEWARE

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### ABSTRACT

Myalgia is a common symptom in patients with Dengue fever. However, acute rhabdomyolysis is a rare manifestation. The precise mechanism of Dengue-associated rhabdomyolysis has not been determined, it is thought likely to be caused by myotoxic cytokines released in response to viral infection, such as TNF and IFN- $\alpha$ . Here we report a case of a 13-year-old boy with Dengue fever, presenting with red urine on day 5 of illness. Together with a decreased platelet count (26 G/L), we initially suspected hematuria but the urinalysis showed no red blood cells. We then thought of rhabdomyolysis causing myoglobinuria, so we ordered diagnostic tests with the following results: CK 1353 U/L, GOT 361 U/L, GPT 90 U/L. The patient was given intravenous fluids and oral oresol to control urine output. Urine color faded and blood CK concentration returned to normal after 13 days. Rhabdomyolysis is rare in dengue fever but requires proper diagnosis and management to prevent acute kidney injury - a life-threatening complication.

**Keywords:** *Rhabdomyolysis, red urine, Dengue fever.*

### I. INTRODUCTION

Dengue fever is an acute infectious disease caused by the Dengue virus, which

can be transmitted from person to person through the bites of infected mosquitoes, mainly *Aedes aegypti*. According to WHO, globally there are about 50 million cases diagnosed with Dengue fever 2.5 million people die from it every year and most of the severe and deceased cases are children under 15, especially infants under 1 [1].

Disease onset is usually acute, with a variety of clinical manifestations, from no symptoms to severe shock and multiple organ failure. Besides common complications, clinicians should also pay attention to rare ones such as mono- or poly-neuropathy, Guillain-Barré syndrome, cardiomyopathy, and acute rhabdomyolysis [2], [3].

Acute rhabdomyolysis (AR) is characterized by the rapid dissolution of skeletal muscle cells and the release of its components into the circulation. It is related to some viral infections, namely influenza, HIV, Coxsackie virus, and CMV, which are quite common and have been described comprehensively in previous studies [4], [5]. However, AR has rarely been seen in Dengue fever, in which the exact mechanism is still poorly understood. Experimental studies have shown that the Dengue virus has a high affinity with human skeletal muscle cells, and high transmissibility as well as replicability [6]. Another hypothesis has been proposed highlighting the role of

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**Date of receipt:** 19/2/2024

**Date of scientific judgment:** 15/4/2024

**Reviewed date:** 22/4/2024

immunological processes, which release cytokines, especially TNG and INF- $\alpha$ , resulting in skeletal muscle cell destruction [5], [7]. Patients with AR are at increased risk of electrolyte disorder, acidosis, coagulation disorder, acute kidney injury (AKI), and even death [8]. Therefore, we need to remind ourselves of this uncommon complication in Dengue fever to recognize and manage it promptly and appropriately.

Here we report a 13-year-old boy diagnosed with Dengue fever in whom AR occurred on the fifth day. We quickly identified the condition then initiated treatment and closely monitored the patient. After 5 days of inpatient management, the symptoms and signs were significantly alleviated and no further complications were observed, so we discharged the patient.

## II. CASE REPORT

A 13-year-old healthy boy initially presented with continuous fever, and muscle pain but not affecting physical activities. There were no other symptoms, so the patient took 1 tablet of paracetamol 500 mg, 4 times a day at home. After one day, he was taken to a private clinic, and blood tests came back with Dengue NS1 (+), Dengue IgM (+), Dengue IgG (-), normal platelet count (PLT) (160 G/L), then he was diagnosed with Dengue fever. He continued to take medication at home with paracetamol and 2 liters per day of oresol. On the fifth day, continuous fever still persisted, red urine

appeared with no lower urinary tract symptoms, and complete blood count showed low PLT (26 G/L), so he was admitted to the Pediatric Center, Bach Mai Hospital on 05 November 2021.

Our physical examination showed that he had a high fever (39°C), high pulse rate (109 BPM), normal blood pressure (110/65 mmHg), normal respiratory rate (23 breaths/minute), SpO<sub>2</sub> 98%; mild pain in the hypogastrium, red urine with no blood clots (Figure 1A), no subcutaneous and mucosal bleeding. No abnormal signs were found in other organs. Initially, we thought of hematuria due to reduced platelet count, or hemorrhagic cystitis due to infection, so we ordered some lab tests and imaging; and got the following results: (1) blood tests: PLT 33 G/L, white blood cell (WBC) count of 9 G/L, CRP of 4.32 mg/L; (2) urinalysis: 70 WBC/ $\mu$ L, 80 red blood cells (RBC)/ $\mu$ L, pH 5.0; (3) abdominal ultrasound: thin bladder wall, clear urine; (4) normal results from other tests (coagulation, electrolyte). Regarding 80 RBC/ $\mu$ L in the patient's urine, it wasn't sufficient to be considered macrohematuria, so we thought of AR resulting in myoglobinuria and ordered more tests which came back with (1) urine cytology: 7 RBC/ $\mu$ L (normally < 10), 30 WBC/ $\mu$ L (normally < 28); (2) blood chemistry investigation: CK 1353 U/L, GOT 361 U/L, GPT 90 U/L, urea 4,4 mmol/L, creatinine 72  $\mu$ mol/L.



**Figure 1.** Patient's urine color on the fifth (A) and sixth (B) day of disease

With the diagnosis of AR due to Dengue virus, our patient continued to take paracetamol when having the fever and drink oresol. We also put him on IV and monitored his urine output for fluid management. One day after hospitalization, the fever was resolved, his urine darkened to a coke-like color (Figure 1B) then slowly returned to

normal in about 3 days. After 5 days, with nothing abnormal revealed in our thorough physical examination, and PLT gradually rising in the blood test results (Table 1), we decided to discharge the patient. Eight days later, he returned to have a checkup, which showed normal levels of CK, GOT, and GPT.

**Table 1.** Changes in some blood test results

Tests	02 Nov	05 Nov	05 Nov	07 Nov	08 Nov	18 Nov
Platelet (G/L)	160	26	33	54	115	576
White blood cell (G/L)	5,6	7,2	9,0	8,7	7,8	4,8
Hemoglobin (g/L)	125	126	126	94	99	104
Hematocrit (%)	34,8	36,2	35,0	26,0	28,0	30,8
CK (U/L)			1353		1440	67,0
GOT (U/L)			361		252	15,8
GPT (U/L)			90		186	46,1

### III. DISCUSSION

Red urine on the fifth day of Dengue fever is a very special condition in this case. Clinicians facing this need to quickly find out whether it is macrohematuria, hemoglobinuria, myoglobinuria, or caused by recent medications or food. In the case of Dengue fever with PLT 26 G/L, macrohematuria was our first suspect; however, physical examination and other assessments did not support that idea: (1) he was hemodynamically stable, had no signs of anemia and bleeding; (2) his urine was red but clear and free of blood clots; (3) urinalysis shown 80 RBC/ $\mu$ L.

Urinalysis is a simple test that can be performed in every healthcare facility to give a general view of the patient's condition. However, it must be noted that the results are obtained from semi-quantitative measurements, which analyze urine test strips based on reflective photometry. These strips are designed to detect heme in urine, which means they cannot differentiate between RBC, hemoglobin, and myoglobin since they all contain heme. Therefore, we ordered urine cytology, and the result of 7 RBC/ $\mu$ L (normally < 10) ruled out the possibility of hematuria. Furthermore, the patient's hemoglobin level was 125 g/L at hospitalization (05 November 2021), which was in the normal range and very close to the previous result (126 g/L) obtained at the private clinic on 02 November 2021, so we excluded intravascular hemolysis resulting in hemoglobinuria.

AR causing myoglobinuria also leads to red urine, or sometimes darker color like coke. In our case, with the patient having pain in the muscle, red urine, and elevated CK (1353 U/L) – an enzyme abundant in skeletal muscle cells, we made the diagnosis

of AR. High total CK in blood is a sensitive marker and is often assessed when AR is suspected [8], [9]. No absolute threshold of CK has been defined; however, it is usually agreed that when CK exceeds 5 times its normal level, together with suggestive clinical findings, a diagnosis of AR can be made [8].

Various possible causes can lead to AR, such as muscle injury, prolonged immobilization, myopathies, electrolyte disorder, intoxication, certain medications, or infections. Although we couldn't perform other tests to rule out other viruses, with our patient's history and clinical features (no history of injury, hemodynamically stable, no other medication apart from paracetamol and oresol), we still suspect that Dengue virus was the culprit.

AR results in the sudden release of cellular components into the circulation, which can lead to severe conditions such as electrolyte and acid-base disorders, coagulation disorders, and especially AKI [8]. Myoglobin released from skeletal muscle cells will accumulate in renal tubules, then interact with Tamm Horsfall protein in the urine to cause precipitation obstructing the tubules. Additionally, in AR, renal tubule cells are also damaged due to reduced perfusion and intrarenal vasoconstriction [4]. Other causes are responsible for 13 – 50% of AKI in AR [4]. Patients with Dengue fever already have reduced circulatory volume, especially those showing signs of shock, which are a risk factor of AKI, and when combined with AR, the risk is significantly higher. According to Lee IK *et al* (2009), the mortality rate in Dengue fever patients with AKI can be up to 60% [10]. Therefore, timely diagnosis and management of AR is

crucial to help prevent AKI and improve the prognosis.

Regarding CK in blood, a particular level marking notably increased risk of AKI has not been defined. Sargeant *et al* (2013) reviewed 7 adults with AR related to Dengue fever reported globally up until that point and showed that CK levels ranged from 5000 to 156900 U/L; also, in 4 patients who developed AKI, the lowest CK level measured was 5000 U/L [11]. Our patient's CK level was 1353 U/L when admitted, which was much lower compared to those, yet it was quite close to that of a 16-year-old male patient, which was 1549 U/L, in Nakamura's report (2015) [12]. AKI didn't develop in either of these two young patients.

Fluid therapy is fundamental in the management of AR patients with or without AKI. Treatment must be started as soon as possible, with the fluid amount and administration method depending on the severity of AR, AKI, and vital signs [8]. Besides, fluid therapy is generally the first choice in managing Dengue fever [1]. In our case, after making the diagnosis of Dengue fever complicated with AR, we quickly administered fluid with IV Ringer Lactate and oral oresol. The condition greatly improved, AKI was successfully prevented, and our patient was discharged after 5 days. Lab tests came back with everything in the normal range when the patient returned one week later for a checkup.

#### IV. CONCLUSION

Although AR is a rare complication of Dengue fever, it can result in severe consequences, especially AKI. During clinical practice, physicians need to pay attention to this condition and assess patients thoroughly to avoid missed diagnoses, especially in those

with muscle pain and red urine. In such scenarios, urinalysis and blood CK measurement can help clinicians quickly diagnose AR and initiate proper management.

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