SUBMITTED 2 APR 24
REVISION REQ. 2 JUN 24; REVISION RECD. 3 JUL 24
ACCEPTED 1 AUG 24
ONLINE-FIRST: OCTOBER 2024
DOI: https://doi.org/10.18295/squmj.10.2024.059

Severe Hemolysis in Glucose 6 Phosphate Dehydrogenase Deficiency Secondary to Dengue Fever

Analysis of 3 cases from Oman

***Antara Gokhale,[1] Huda Al Khalili,[1] Mahmoud Al Abri[2]**

Departments of [1]Anesthesia & Adult Critical Care and [2]Clinical Hematology, Royal Hospital, Muscat, Oman

**Corresponding Author's e-mail: gokhaleantara@gmail.com*

Abstract

Dengue is a viral fever transmitted by Aedes species of mosquitoes. Globalization has led to worldwide spread of DF including Oman. High incidence of Glucose 6 phosphate deficiency (G6PD) is present in the population, often undiagnosed. We report three patients admitted in tertiary care hospital in Muscat, Oman with Dengue Fever (DF) that later triggered hemolysis. It proved fatal in one case and caused irreversible renal damage requiring dialysis in other. Both DF and G6PD deficiency can cause bleeding. Both need supportive treatment and avoiding incriminating factors. G6PD deficiency with concomitant viral infections have been reported to increase morbidity and mortality. Hemolysis triggered due to DF in G6PD deficient has not be reported in literature. If the clinical course or hemolytic pattern in DF deviates from expected, an associated hemolytic disorder should be considered especially in regions with high prevalence.

Keywords: Dengue Fever; Glucose 6 Phosphatase Dehydrogenase Deficiency; Hemolysis; Organ Dysfunction.

Introduction

Dengue fever (DF) is an arthropod borne viral fever reported worldwide. Though relatively new to Middle -east region there has been a steady rise in DF cases annually. Initially a disease of immigrant population, DF is now indigenous in Oman since 2013. [1] DF is usually self-limiting with fever followed by thrombocytopenia, mild hemolysis with hematuria and bleeding. [2]

Severe cases may progress to Dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) which can be fatal. [3, 4]

Viral infections are known to trigger intravascular hemolysis in G6PD deficient patients. [5,6,7, 8] Dual effect of hemolysis contributed by DF and G6PD can prove fatal.

During the DF outbreak in May 2023, we observed three patients admitted in our intensive care unit (ICU) who continued to show features of hemolysis even after improvement of DF induced thrombocytopenia. All three were unaware of their G6PD deficient status. As search for probable causes of hemolysis proved negative it was concluded that the oxidative stress produced by DF triggered hemolysis in these cases. All patients showed elevated liver enzymes, raised hemolytic markers, methemoglobinemia and peripheral blood film suggestive of hemolysis. First patient had elevation of liver enzymes, developed hepatic encephalopathy and responded to supportive therapy. The other two patients showed elevated methemoglobin levels. One of them showed persistent hematuria, developed renal failure and required long term dialysis. Third patient developed acute hepatic failure requiring multiorgan support including plasma exchange. Organ dysfunction, permanent organ damage and death have all been described as complications of G6PD induced hemolysis. [6,7,8, 9] Delay in diagnosing the G6PD deficient status resulted in deviation of management strategy. Though treatment in both DF and G6PD is supportive, awareness of later will help to decrease morbidity and mortality.

Case 1

A 47 years diabetic, hypertensive male was admitted in with four days history of fever, myalgia, abdominal pain and reduced urine output. Clinically, patient had hypotension and required inotropes along with fluid resuscitation. Blood investigations showed thrombocytopenia,

transaminitis, and acute kidney injury (AKI). (Table1) Dengue RNA -PCR flagged positive. Patient responded to supportive care with hydration, fluid intake -output and hemodynamic monitoring. By fourth day, platelet count and AKI improved. Patient continued to feel unwell and was drowsy. Clinical examination showed evidence of encephalopathy with right hypochondriac and epigastric tenderness. A drop in hemoglobin with near normal MCHC (Mean Cell Hemoglobin Concentration) and MCH (Mean Cell Hemoglobin) values, elevated Serum lactate Dehydrogenase (LDH) and normal haptoglobin suggest acute hemolysis. Hemoglobin levels dropped significantly (Table 1). Blood film showed microcytic hypochromia, blister cells, elliptocytes and few tear drop cells suggestive of hemolysis. Ultrasound abdomen showed fatty liver. History of exposure to medications, alternative herbal therapies, infections and travel was negative. As both clinical and laboratory parameters associated with dengue infection were improving the acute hepatic derangement was thought to be triggered secondary to DF. Patient was found to be G6PD deficient. Serum glucose, hepatic and renal hemogram along with hydration were closely monitored for ten days till normalization.

Case 2

A 52-year-old diabetic gentleman was referred from health center with history of fever followed by thrombocytopenia, AKI, transaminitis and low urine output. Dengue RNA PCR was positive prior to admission. Patient was noted to have bradycardia, oliguria and hematuria with steady reduction in serum creatinine and eGFR (estimated Glomerular filtration Rate). By day 3 of admission, oliguria and hematuria persisted despite optimization of hemodynamic parameters. A drop in hemoglobin disproportionate to hematuria was noted requiring blood transfusions (3gm/dl). Platelet count however improved. He developed pulmonary edema requiring noninvasive ventilation (NIV). ECHO (Echocardiography) showed calcified aortic valve with moderate aortic stenosis (EF-55%) and no regional wall motion abnormality. Cardiac cause of edema was ruled out.

Blood gas analysis showed rising lactates and methemoglobinemia (Table 2). The methemoglobin levels rose from normal values at admission to 15% before normalizing on 10 days. Raised bilirubin, LDH and low haptoglobin along with peripheral blood film suggested hemolysis. Based on this G6PD levels was assessed and found low.

Patient required blood transfusions and oxygen therapy and intermittent hemodialysis. Hospital stay was complicated by health care associated pneumonia that required intubation and mechanical ventilation. Management was primarily supportive with avoiding incriminated medication. As the hemolysis stopped, methemoglobin levels normalized. Patient was successfully extubated and discharged. However, he had irreversible renal failure and became dialysis dependent.

Case 3

A 56 years old male with no known comorbidities, presented with one day history of self-limiting fever. Ten days later he visited the regional hospital with generalized fatigability and myalgia. He was afebrile but icteric and was admitted for further evaluation. Initial blood tests showed thrombocytopenia, elevated liver enzymes, raised ammonia and deranged kidney function. Dengue fever was suspected. Within hours of admission patient showed features of encephalopathy, suggesting acute liver failure. In view of rapidly worsening liver functions, he was transferred the next day to our unit for possible liver transplant. He was intubated prior to transfer for low level of consciousness and needed inotropes. CT head was normal. On arrival to the ICU he was on vasopressors, ventilator support and needed renal replacement therapy. Dengue PCR meanwhile flagged positive. A diagnosis of Dengue related acute liver failure was made and treatment started. Plasma exchange was initiated to support liver. [10. 11] Adequate partial pressure of oxygen in blood gas analysis despite low peripheral saturations (88%) was noted. Elevated methemoglobin levels explained this. (Table3) Raised LDH, low haptoglobin and blood film with occasional spherocytosis and Howell- Jolly bodies confirmed hemolysis. Patient was found to be G6PD deficient. Supportive treatment was continued. However, the patient was already in multiorgan failure and expired within 48 hours of admission. G6PD related hemolysis triggered by Dengue fever was suspected.

Hospital ethics committee clearance was obtained after approval of patients for publication.

Discussion

Dengue fever (DF) is an arthropod borne viral disease reported globally. In majority of cases the presentation is like other viral fevers. Within 1 -10 days of infection, fever may be followed with thrombocytopenia and hemolysis with a self-limiting course. A small percentage progress to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) which can be fatal and characterized by bleeding from various sites, acute kidney injury (AKI), liver dysfunction, deranged coagulation and third space fluid extravasation [2,3,4 6]

Initially considered a disease of tropical and subtropical regions, the disease is now reported globally due to easy movement of population and rapid urbanization. Though the climatic conditions in Middle-east are not suitable for spread of DF it has been declared endemic in many countries in the region. [6] Large immigrant population is another major contributory factor. Since 2008 a steady rise in number of DF is being reported from Oman. Since the 2018 DF has been found to be indigenous. The incidence of 2.34 per 100000 population is reported as of 2022. [1, 5]

Patients with severe illness, documented bleeding, thrombocytopenia or clinical manifestations of organ dysfunction are admitted to hospital. Severe cases may require intensive care admission and multiorgan support.

During the recent outbreak in early 2023 amongst the patients admitted with DF to our ICU it was noticed 3 patients deviated from usual course of DF. They had evidence of hemolysis despite normalization of platelets. All three showed elevated levels of methemoglobin and were found to be G6PD deficient.

Raised conjugated bilirubin disproportionate to enzyme elevation, renal failure secondary to hemoglobinuria and massive intravascular hemolysis, associated methemoglobinemia and fatal liver failure are all described as manifestations of G6PD deficient hemolysis. [3, 5, 7, 8 ,9).

The incidence of G6PD is documented at 25% in Omani male population and 10% in female population. [1] Being X linked recessive disorder males manifest the symptoms. Females may

show evidence of hemolysis only if homozygous. Not all are aware about their deficient status. [1, 2]

The enzyme G6PD is involved in the pentose mono phosphate shunt. It helps glucose 6 phosphatase to reduce nicotinamide adenine dinucleotide phosphate (NADP) which in turn helps in scavenging oxidative metabolites in red cells. Its deficiency thus increases the free oxygen radicles which damage the cellular structures. Iron in the heme of RBCs is in the ferrous form (Fe^{+2}). This is oxidized to ferric form (Fe^{+3}) which is poor in oxygen uptake leading to hypoxemia. Methemoglobinemia is often seen in patients with G6PD. [3] Hypoxemia occurs when its levels exceed 10%. [5]

There are more than 300 variants of the genes and severity of hemolysis depends on the level of enzyme activity. [3,12] Based on level of enzyme deficiency and severity of hemolysis, WHO has classified G6PD variants in I-V. Those with low enzyme levels produce massive hemolysis with various triggers, while some like G6PD (A-) produce hemolysis in presence of oxidative stresses only. Certain variants cause hemolysis of old RBCs in the presence of oxidative stress.

Most patients are asymptomatic and may develop acute hemolysis within 24-72 hours after exposure to triggers. The episodes are usually self-limiting for 8-14 days when the new RBCs replace the old ones and blood transfusions are rarely required. In some cases, chronic hemolytic anemia persists. [9]

G6PD is required to maintain the redox potential in the EMP pathway. The well-known stressors are drugs, chemicals, infections and fava bean ingestion. There are case reports where G6PD deficient patients when affected by certain viral infections -influenzas, hepatitis, HSV and recent Covid -19 have been shown to have increased morbidity. [2, 3, 4, 11, 12] In presence of oxidative stressors, the RBCs especially the older ones are unable to generate adequate NADPH which is a percussor for glutathione. Decreased glutathione decreases the ability of RBCs to metabolize oxidant radicles and their breakdown increases. [5] Increased incidence of diabetes has also been seen in these patients. The oxidative stressors may cause methemoglobinemia which impairs tissue oxygenation and impairs cellular functioning. [6]

Patient with hemoglobinopathies may suffer from effect of hemolysis due to disease itself and that induced by G6PD deficiency enzyme.

Conclusion

The two conditions Dengue fever and G6PD induced hemolysis may overlap and as the duration of disease progresses, complicate diagnosis and line of therapy. Treatment of both DF and G6PD is supportive. Awareness of deficient status may help to avoid potential triggers and guide supportive treatment, thereby reducing the potential morbidity and mortality.

Authors' Contribution

AG contributed to conception and design, acquisition of data, analysis and interpretation of data and drafting the article/revising it critically. HAK contributed to conception and design, interpretation of data and revising the manuscript critically. MAA contributed to analysis, interpretation of data and revising the manuscript. All authors approved the final version of the manuscript.

References

1) Al-Riyami A , Ebrahim GJ .Genetic Blood Disorders Survey in the Sultanate of Oman J Trop Pediatrics 2003;49(1)1-20. PMID: 12934793

2) Schaefer TJ, Panda PK, Wolford RW. Dengue Fever, StatPearls Publishing; Jan 2024, PMID: 28613483 Bookshelf ID: NBK430732

3) Laslett N, Hibbs J, Hallett M, Ghaneie A, Zemba-Palko V. Glucose-6-Phosphate Dehydrogenase Deficiency- Associated Hemolytic Anemia and Methemoglobinemia in a Patient Treated with Hydroxychloroquine in the Era of Covid -19. Cureus. 2021May25;13(5): e15232. Doi:10.7759/ cureus.15232. PMID: 34178542 PMCID: PMC8223605

4) Al Awaidy ST, Khamis F, Al-Zakwani I, Al Kindi S, Al Busafi S, Al Sulaimi K et al Epidemiological and Clinical Characteristics of Patients with Dengue Fever in a Recent Outbreak in Oman: A Single Center Retrospective-cohort Study. Oman Med J 2022.Nov30;37(6): e452. Doi: 10.5001/omj.2023.57. ecollection2022 Nov. PMID: 36458248. PMCID: PMC9669402

5) Richardson SR, O'Malley GF. Glucose-6-Phosphate Dehydrogenase Deficiency StatPearls Publishing; 2024 Jan. PMID: 29262208. Bookshelf ID: NBk470315

6) Al Balushi L, Al Kalbani M, Al Manji A, Amin M, Al Balushi Z, Al Barwani N et al. A second local dengue fever outbreak: A field experience from Muscat Governorate in Oman, 2022. IJID 2023. 1: 7:237-241. doi: 10.1016/j.ijregi.2023.03.015. eCollection 2023 Jun. PMID: 37187798 PMCID: PMC10176167

7) Kamani L, Shaikh H, Khemchandani AK. Fulminant Hepatic Failure in Glucose -6-Phosphatase Dehydrogenase (G6PD) Deficient patients caused by Hepatitis infection: A Single Disease with Different Spectrums. Case Reports. Cureus. 2020 Dec 25;12(12): e12276. doi: 10.7759/cureus.12276. PMID: 33510983 PMCID: PMC7828574

8) Karki P, Malik S, Mallick B, Sharma V, Rana SS. Massive Hemolysis Causing Renal Failure in Acute Hepatitis E Infection. J Clin Transl Hepatol. 2016 Dec 28;4(4):345-347. doi: 10.14218/JCTH.2016.00042. Epub2016. Nov23 PMID: 28097104. PMCID: PMC5225155

9) Abdullah NH, Mohammad N, Ramli M, Gazali WS. Hemolytic anemia precipitated by dengue fever. BMJ Case Rep 2019 Aug28;12(8): e226760. Doi :10.1136/bcr-2018-226760. PMID: 31466966. PMCID: PMC6721012

10) Arunpriyandan V, Sundaresan KT. Fulminant hepatic failure in Dengue Fever without Plasma leakage: A case report. Case Reports. Cureus.2022. Apr 8; 14(4): e 23964 doi: 10.7759/cureus. 23964. eCollection 2022 Apr. PMID: 35547461 PMCID: PMC9090125

11) Thanh NT, Dat NT, Thinh TC, Phuong NTM, Thanh MTH, Bao NT et al. Therapeutic plasma exchange and continuous renal replacement therapy in pediatric dengue associated acute liver failure: A case series from Vietnam. Transfus Apher Sci. 2023 Apr;62(2):103617. doi: 10.1016/j.transci.2022.103617.Epub 2022 Nov 28 PMID: 36522271

12) Yang HC, Ma TH, Tjong WY, Stern A, Chiu DTY. G6PD deficiency, redox homeostasis, and viral infections: implications for SARS-CoV-2 (COVID-19) Free Radic Res. 2021 Apr;55(4):364-374. doi: 10.1080/10715762.2020.1866757. Epub 2021 Jan 6 PMID: 33401987 PMCID; PMC7799378

241 **Table 1**: Blood Results of patient1

Investigation	Day 0 Day of admission	Maximum change (day5-7)	Discharge home Day10
Dengue	+ve		
G6PD	171 (deficient)		
Hemoglobin(gm/dl)	13.8	9.7	9.3
Platelets10*9/L	237	85	240
WBC 10*9/L	9.2	12	9
Methemoglobin (0-1.5%)	1.2	5.9	2.6
Sr Creatinine(62-110(µmols/l)	170	104	71
eGFR ml/min/1.73m2	43	77	>90
ALT (10-40IU/L)	114	129	59
AST (0- 34U/L)	-	343	99
Bilirubin -T(5-21µmols/l)	29	81	55
Conjugated bilirubin (0-5µmols/l		55	
LDH (126-246IU/L)	3189		
Haptoglobin(400-2800mg/l))		100	
Sr Sodium (135-145 mmol/l)	129	140	141
Sr Potassium (3-5.5 mol/l)	3.8	4	3.4
Sr Urea (2.6-6.2 mmol/l)	12.9	8.0	6.4

242

243 **Table 2:** Blood results of patient 2 along with interventions

Investigation	Day 0	Maximum admission values (Day5-15)	At discharge Day 26	Interventions
Dengue	+ve			
G6PD		150		
Hemoglobin gm/dl	14	11		Blood transfusion
Platelets 10*9/L	55	113	163	
WBC 10*9/L	11	10	5.1	
Methemoglobin(0-1.5%)	1.2	7.3 (day10)	0.09	
Urea (2.6 -6.2 mmol/l)	9.2	19 (day 8)	6.3	
Creatinine(62-110µmols/l)	33	361(day8)	431	Dialysis at 3 months
eGFR ml/min/1.73m2	56	17	13	
ALT (10-40IU/L)	47	806 (day-6)	27	
AST (0-34 IU/L)		5564 (day 6)		
Bilirubin -T(µmols/l)	22	512 (day10)	80	
Conjugated bilirubin		426 Day-10)		
Ammonia (11-32(µmols/l)		136 (day- 6)		
PT/INR (9.8-11.9s)	13.6/1.22	13.8	13.4	
APTT (26.4-38.9s)	58	41	40	
Fibrinogen (1.6-4g/l)	2.02	1.24	2.56	
Haptoglobin (400-2800IU/L)		176		

LDH (126-246iU/L)		6459 (day-10)	358	

244

245 **Table 3**: Blood results of patient 3 and intervention

Blood Tests	Day 0	Day1	Day-3	Interventions
Dengue RNA	+ve			
G6PD	289 (Deficient)			
Hemoglobin(gm/dl)	10	8	7	Blood transfusion
Platelets (10*9/L)	79	71	63	
WBC910*9/L	35	27	21	
Methemoglobin (0-1.5%)				
Creatinine(62-110µmols/l)µ	332	265	222	On dialysis
Bilirubin -T(5-21µmols/l)	164	175	243	
Conjugated bilirubin(µmols/l)	-	-	-	Hemolyzed
ALT (10-40IU/L)	1651		1070	
GGT (0-38 IU/L)	5812			
AST (10-46 IU/L)	5812	Icteric		
PT/INR (9.8-11s)	24/2.39	19/1.9	28/2.9	FFP
APTT (26.4-33.9s)	65	40	55	
Fibrinogen (1.6-4 gm/L)	0.5	<0.5	<0.5	Cryoprecipitate
Haptoglobin (400-2800 mg/L)	320			
LDH (126-246 IU/L)	>7500		>7500	
Ammonia (11-32(µmols/l)	200			

246 *Day 0 - Day of admission to ICU*

247 *WBC- White Blood cells, GGT- gamma glutamyl transferase, ALT- Alanine transferase, AST-*

248 *Aspartate aminotransferase. LDH – Lactate Dehydrogenase in serum, PT- Prothrombin time.*

249 *APTT- Activate Partial thromboplastin time, e GFR- estimated Glomerular filtration rate.*