RESEARCH ARTICLE

The severity of acute viral hepatitis in patients with glucose-6-phosphate dehydrogenase deficiency: a case-control study

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Abstract

Objective: To compare outcomes and severity parameters in patients with acute viral hepatitis and those with acute viral hepatitis and glucose-6-phosphate dehydrogenase deficiency.

Method: The retrospective, case-control study was conducted at Aga Khan University Hospital, Karachi, and comprised data from June 1, 2016, to January 31, 2022, related to patients with acute viral hepatitis having glucose-6-phosphate dehydrogenase deficiency in group A, and patients with acute viral hepatitis without G6PD deficiency in control group B. Data was analysed using SPSS 19.

Results: Of the 27 male patients, 9 (33.3%) were in group A, with a mean age of 28.89 ± 6.7 years, while group B had 18 (66.6%) patients, with a mean age of 28.11 ± 8.6 years. There was no female subject in the sample. The haemoglobin levels were lower in group A patients (p=0.06). Total bilirubin, direct bilirubin, serum creatinine, and the length of hospital stay were significantly different between the groups (p<0.05).

Conclusion: Acute hepatitis in patients with G6PD deficiency may present with a more severe course complicated by haemolysis, hyperbilirubinaemia, acute liver failure, and acute kidney injury. Early recognition of G6PD deficiency is essential for appropriate monitoring and prevention of complications.

Key Words: Hepatitis, Viral, Glucosephosphate dehydrogenase deficiency.

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Introduction

Acute viral hepatitis is a significant cause of morbidity and mortality globally. Recent studies demonstrate a shifting trend in the incidence of hepatitis A, which previously targetted the paediatric population, but now affects individuals of all age groups. South Asian countries carry a significant burden of the disease due to unhygienic food handling. Acute viral hepatitis is a subclinical infection, and it resolves without complications in most cases.[1] The global burden of viral hepatitis is about 2.3 billion, and, according to World Health Organisation (WHO) estimates, 1.4 million new cases of hepatitis A virus (HAV) and 20 million cases of hepatitis E virus (HEV) are reported annually globally.[2]

Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme that protects the red blood cells (RBCs) against oxidative damage. G6PD deficiency affects more than 400 million people worldwide. It clinically presents in adults as haemolytic anaemia. These manifestations include pallor, jaundice, fatigue, splenomegaly and dark urine.[3] A study on the frequency of G6PD deficiency in some ethnic groups of Pakistan showed that the frequency in young healthy adults, with a non-significant difference among various ethnic groups, was 1.8%.[4]

A case report mentions that while HEV is a common cause of acute viral hepatitis, it is seldom fatal and usually presents as a self-limiting infection. However, in patients with G6PD deficiency, it may be associated with complications, such as severe anaemia, haemolysis, renal failure, hepatic encephalopathy and even death.[5] A case-control study revealed that the length of hospital stay (LOS) was nearly three times longer in the study group than in the control group.[6] The association of HAV with G6PD usually leads to exaggerated intravascular haemolysis, hyper-bilirubinaemia and acute renal failure.[7]

To our knowledge, recent literature has limited data on the outcomes of co-morbid G6PD deficiency with hepatitis, and existing studies are at least a decade old.[5-9] The current study was planned to compare outcomes and severity parameters in patients with acute viral hepatitis and those with coexisting G6PD deficiency, and to ascertain whether or not G6PD deficiency influences the prognosis and outcome of the disease.

Materials and Methods

The retrospective, case-control study was conducted at

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Aga Khan University Hospital (AKUH), Karachi, and comprised data from June 1, 2016, to January 31, 2022, related to patients with acute viral hepatitis having G6PD deficiency in group A, and patients with acute viral hepatitis without G6PD deficiency in control group B. Data was retrieved from the institutional Health Management Information Services after approval from the institutional ethics review board and a waiver of informed consent. The cases were identified by reviewing the medical records of all the patients admitted to the gastroenterology service due to symptomatic acute viral hepatitis, like jaundice, vomiting, abdominal pain and markedly elevated bilirubin level, requiring inpatient evaluation. Group B controls were matched for age and gender with group A cases.

All the eligible cases identified were included because, owing to the rarity of the condition, a formal sample size calculation was not feasible. The ratio between groups A and B was kept at 1:2 in order to maximise the statistical power within the available sample. Data of patients with chronic liver disease, haemolytic anaemia due to causes other than G6PD deficiency, coexisting conditions or infections that could cause liver enzyme derangement, incomplete medical records and recent blood transfusion history were excluded.

Patient demographics included age, gender, LOS, and laboratory data. Indication of admission was symptomatic, with patients presenting with fever, jaundice, nausea, abdominal pain, itching and altered mental status. Information on the administration of haemodialysis and complications, including anaemia, encephalopathy and acute kidney injury (AKI), was noted on the basis of written physician notes. All laboratory values were cross-checked with original medical records for accuracy. No formal outlier exclusion was performed, and all the observed values were included in the final analysis.

Data was analysed using SPSS 19. Data was expressed as mean ± standard deviation or frequencies and percentages, as appropriate. Continuous variables were compared between the groups using an independent-samples t-test. $P<0.05$ was considered statistically significant.

Results

Of the 506 patients admitted with acute viral hepatitis, 9(1.77%) were found to have G6PD. In keeping with the 1:2 ratio between group A and group B, the total sample was 27; 9(33.3%) in group A, with a mean age of 28.89±6.7 years, and 18(66.6%) patients in group B with a mean age of 28.11±8.6 years. There was no female subject in the sample. In group A, 1(11.1%) patient presented with acute liver failure due to HEV and was managed conservatively. AKI was common in group A patients 4(44.4%). However, no patient required renal replacement therapy. In group A, 8(88.9%) patients were identified on the basis of unexplained anaemia or haemolysis, while 1(11.1%) patient was a known case. In group B, all 18(100%) patients had normal G6PD levels. Haemolysis was present in 4(44.4%) patients in group A compared to none in group B (Table 1).

Table-1: Intergroup comparison of baseline characteristics and descriptive data.

Percentages/Mean	Viral Hepatitis + G6PD deficiency N=9	Viral Hepatitis only N=18
Age	28.89 (±6.7)	28.11(±8.6)
Gender		
Male	9 (100)	18 (100)
Female	0	0
Symptoms (%)		
Fever	5 (55.6)	12 (66.7)
Nausea	6 (66.7)	15 (83.3)
Jaundice	8 (88.9)	7 (38.9)
Abdominal pain	5 (55.6)	11 (61.1)
Itching	6 (66.7)	0
Altered Mental State	1 (11.1)	0
Anaemia (Haemoglobin 11-14.5g/dl)	5 (55.6)	3 (16.7)
Acute Kidney Injury	4 (44.4)	0
Thrombocytopenia	1 (11.1)	3 (16.7)
Coagulopathy	6 (66.7)	3 (16.7)
Haemolysis (reticulocyte count > 2.5%)	4 (44.4)	0
Acute Liver Failure	1 (11.1)	0
HDU Admission	2 (22.2)	1 (5.6)
Renal Replacement Therapy	0	0
Plasmapheresis	0	0
N-Acetyl cysteine IV	1 (11.1)	3 (16.7)
Previously known as G6PD deficiency	1 (11.1)	-
Alcohol history	0	0
Blood product transfusion	2 (22.2)	0
Outcome		
Discharged	7 (77.8)	18 (100)
Re-admitted	2 (22.2)	0
Expired	0	0
Virus		
A	2 (22.2)	9(50)
E	7 (77.8)	9 (50)
B	0	0
C	0	0

G6PD: Glucose-6-phosphate dehydrogenase, HDU: High-dependence unit.

The haemoglobin (Hb) levels were lower in group A patients (p=0.06). Total bilirubin, direct and indirect bilirubin, serum creatinine, prothrombin time (PT), international normalised ratio (INR) and LOS were significantly different between the groups ($p<0.05$) (Table 2).

Table-2: Intergroup comparison of laboratory data.

Parameters Mean (± SD)	Viral Hepatitis + G6PD deficiency (N=9)	Viral Hepatitis only (N=18)	p Value (<0.05)
Haemoglobin (11-14.5g/dl)	10.74(±6.7)	13.2 (±2.69)	0.06
Platelets (154-433x109 /L)	287.6(±84.3)	230.1(±94.12)	0.13
Creatinine (0.6-1.2mg/dl)	1.37(±0.87)	0.84(±0.24)	0.02
Total bilirubin (0.1-1.2mg/dl)	45.3(±14.9)	6.03(±3.64)	<0.01
Direct bilirubin (0-0.2mg/dl)	34.3(±9.79)	5.14(±3.14)	<0.01
Indirect bilirubin (0.1-0.8md/dl)	11.0(±6.88)	0.8(±0.76)	<0.01
ALT (<45 IU/L)	2675.8(±1949.6)	2029.1(±1210.5)	0.2
AST (<35 IU/L)	2052.4(±2960.0)	1627.6(±1387.9)	0.6
Prothrombin Time (9.3-12.8 sec)	17.9(±7.59)	12.85(±2.42)	0.01
INR (0.9-1.2)	1.73(±0.80)	1.22(±0.25)	0.02
Length of hospital stay (Days)	4.11(±1.45)	2.61(±1.33)	0.01

G6PD: Glucose-6-phosphate dehydrogenase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, INR: International normalised ratio.

Discussion

In literature, mainly individual case reports are published [5,7]; to our knowledge, this retrospective case-control study represents one of the largest cohorts of acute viral hepatitis patients with G6PD deficiency reported to date. Mild haemolysis is a clinically insignificant consequence of acute hepatitis.[8] Hb levels rarely drop >1-2g/dL until and unless there is simultaneous bone marrow suppression, blood loss, or severe haemolysis.[9] G6PD deficiency is an X-linked recessive genetic disorder that may promote excessive RBC lysis secondary to oxidative stress.[8] The reduced glutathione levels in RBCs are due to reduced nicotinamide-adenine dinucleotide phosphate (NADPH) salvation via glucose metabolism.[10] Examples of oxidative stressors include infections or certain drugs, like sulfonamides.[11] There is a scarcity of studies describing the increased severity of acute hepatitis in patients with concomitant G6PD deficiency.[12-13] G6PD deficiency and hepatitis share common ground in Southeast Asia, and it is for this reason that they have a high likelihood of occurring in the same patient.[14-15] Specific Mediterranean populations have been reported to be suffering from a severe variant of G6PD deficiency.[16-17]

The current cohort consisted of an all-male population of 27 patients presenting with acute viral hepatitis A and E, out of whom 9(33.3%) were G6PD-deficient. Hepatitis E was the common virus in the G6PD-deficient group. Among G6PD-deficient patients, 44.4% had haemolysis, but the entire group exhibited significantly higher mean bilirubin (total, direct, and indirect) levels, lower mean Hb levels, and prolonged LOS. These findings are consistent with previous studies.[9,12,13,18] One study reported a higher rate of haemolysis (44%) and significantly longer PT in its G6PD-deficient group.[11] PT in the current population did differ significantly between the two groups. One study reported higher platelet counts in its G6PD-deficient group, but no significant difference was noted in LOS between the deficient and non-deficient groups.[8] Acute tubular necrosis (ATN) leading to AKI and possibly death following haemolysis is a common occurrence in patients with acute hepatitis and hyperbilirubinaemia.[4-5] Yet, significant renal dysfunction in these patients is rare .[12-13] AKI in the current G6PD-deficient group was significantly higher than in patients without G6PD deficiency.

The current study has limitations due to a smaller sample size. This was because of the extraordinary rarity of coexisting acute viral hepatitis and G6PD deficiency. The absence of a formal sample size calculation due to total population sampling and the small number of cases may limit the statistical power of the study and the generalisability of its findings. Besides, all the patients were male. Therefore, the study could not analyse the severity in females. This was due to the rarity of the disease in females and the under-reporting of female patients with G6PD deficiency. Also, G6PD deficiency in the study was diagnosed based on clinical suspicion, which may have introduced bias. The presence of wide variability in laboratory parameters resulted in large standard deviations. However, exclusion of extreme values was avoided to prevent bias in this small cohort. Because the G6PD group was small (n=9), the study used an independent-samples t-test to compare the groups, which is a reasonably robust method even when the data is not perfectly normal. However, due to the small sample size, the results should be interpreted with caution.

Despite the limitations, however, the data suggest that hyperbilirubinaemia in patients with acute hepatitis A and E infections should prompt observation for renal injury, hepatic failure and haemolysis. Monitoring of neurological status by GCS (Glasgow coma scale)[19], urinary output, electrolyte imbalance, and avoidance of hepatotoxic drugs, sedatives and nephrotoxic drugs to precipitate acute liver failure and AKI is crucial. Should haemolysis occur, one should consider G6PD deficiency as a possibility in acute viral hepatitis. Checking G6PD levels in such patients is of critical value, and the patients should receive detailed counselling regarding the disease and the factors that can lead to haemolysis in the future. Additionally, universal vaccination against hepatitis A and E may reduce the overall burden of complicated infections.

Conclusion

Acute hepatitis in patients with G6PD deficiency may present with a more severe initial course complicated by haemolysis, hyperbilirubinaemia, acute liver failure and

acute kidney injury. Such patients require close monitoring for neurological status and renal function. Early assessment of G6PD levels is essential for timely diagnosis, counselling and prevention of future complications.

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OA & ZG: Data collection and drafting.
OP: Concept, design, questionnaire design, supervision and final approval.