ORIGINAL ARTICLE

An audit of the precipitating factors for haemolytic crisis among glucose-6-phosphate dehydrogenase-deficient paediatric patients

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Background Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most common genetic enzyme deficiencies leading to haemolytic anaemia. This study aimed to investigate the precipitating factors for haemolytic crisis in G6PD-deficient paediatric patients in Jordan.
Method A retrospective study of data from the records of 258 paediatric patients admitted to a major paediatric hospital in North Jordan from January 2001 until April 2007. Patients included were G6PD-deficient children who were admitted to the hospital secondary to an episode of haemolytic anaemia.
Results Of 258 paediatric patients, 244 (94.2%) had developed a haemolytic episode secondary to ingestion of fava beans. The remaining 14 children (5.8%) developed a haemolytic episode triggered by other factors, such as drugs and upper respiratory infections.
Conclusion Fava bean ingestion is the major precipitating factor for haemolytic anaemia episodes among G6PD-deficient children in Jordan.

INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is considered to be one of the most common genetic enzyme abnormalities,[1–3] affecting more than 400 million people worldwide.

G6PD is a vital enzyme found in body cells. It is responsible for catalysis of the first step in the oxidation of glucose-6-phosphate to 6-phosphogluconate. However, the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) is produced at the same time.[4–7] NADPH is important for the stability of glutathione (GSH) and other proteins in the reduced form to maintain the intracellular redox potential and protect cells from oxidative stress.[8–10] Haemolysis of G6PD-deficient red blood cells usually results from an increased susceptibility to oxidative damage; in addition, the production of NADPH decreases and this leads to inadequate regeneration of the reduced GSH.[11]

The most common clinical manifestations in patients with G6PD deficiency are neonatal jaundice and acute haemolytic anaemia, which is precipitated by several factors, such as infections, drugs and ingestion of fava beans.[9,11–13]

Favism is a potentially life-threatening haemolytic anaemia that results from the ingestion of fresh, frozen, cooked, raw or dried fava beans in G6PD-deficient patients.[11,12] In determining the toxic factors present in fava beans, the pyrimidine glycosides (vicine and convicine) have been isolated from fava beans, the aglycons of which (divicine and isouramil, respectively) are responsible for favism induction.[14,15]

G6PD deficiency is an inherited x-linked recessive disorder that usually affects men. In Jordan, G6PD deficiency is a common health problem that usually peaks in spring due to fresh fava beans ingestion. The prevalence of favism has been reported to be 3.6% among the Jordanian population.[16]

In this study, we investigated factors that might contribute to the development of haemolytic crisis in G6PD deficiency patients. To the best of our knowledge this is the first report, at least regionally, to explore the role of fava bean ingestion in precipitating haemolytic crisis in G6PD-deficiency patients.

MATERIALS AND METHODS

All the known cases of G6PD deficiency with a haemolytic crisis (258 patients: 197 [76.4%] men and 61 [23.6%] women) were evaluated. A retrospective approach was used, based on the medical records of those patients admitted to Princess Rahma Teaching Hospital in Northern Jordan secondary to a haemolytic anaemia episode in the period between January 2001 and April 2007. Data were collected through a manually filled questionnaire in which information was obtained from the medical records. Patients included in this research were all children with age ranges from 1 month to 13 years. We classified anaemia into three main categories: severe, moderate and mild, according to the study by Gandapur *et al.*[17]

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Table 1 Prevalence of signs and symptoms presented in glucose-6-phosphate dehydrogenase-deficient patients

Signs and symptoms	*n* (%)
Pallor	252 (98)
Red urine	247 (96)
Jaundice	241 (93.4)
Fever	47 (19.3)
Abdominal pain	45 (18.7)

Table 2 Precipitating factors for haemolysis among sample studied. ($n = 258$)

Precipitating factor	*n* (%)
Ingestion of fava beans	244 (94.2)
NSAIDs* (ibuprofen, diclofenac)	5 (1.9)
URTIs†	3 (1.2)
Co-trimoxazole‡	2 (0.8)
Sulphonamides	
Pollen inhalation	1 (0.4)
Hepatitis	1 (0.4)
Naphthalin	1 (0.4)
Breast feeding	1 (0.4)

*NSAIDs: non-steroidal anti-inflammatory drugs
†URTIs: upper respiratory tract infections
‡Co-trimoxazole: trimethoprim-sulphamethoxazole combination

The questionnaire discussed the main precipitating factors for acute haemolysis (fava, infection, illness, drugs and others). The drugs we searched for were specifically: ibuprofen, diclofenac, co-trimoxazole and nalidixic acid.

We also searched for the most prevalent signs and symptoms at the time of admission, month of admission, presence of family history of G6PD deficiency, admission to paediatric intensive care unit and duration of hospital admissions.

Laboratory tests including complete blood count, total and direct bilirubin, urea, glucose, sodium, potassium and G6PD level were performed at admission.

Statistical analysis was carried out using SPSS version 15.0 for Windows® (SPSS V 15.0, Chicago, IL, USA).

RESULTS

The most prevalent signs and symptoms in G6PD-deficient patients were pallor (98%), red urine (96%), jaundice (93.4%) and fever (19.3%). Only 18.7% of the studied sample suffered from abdominal pain (see Table 1).

Many precipitating factors such as infections, ingestion of certain drugs and diseases can lead to haemolysis in patients with G6PD deficiency.[17–19] With respect to our results, the most common precipitating factor for haemolysis was the ingestion of either dried or fresh fava beans ($n = 244$; 94.2%) followed by ingestion of NSAIDs ($n = 5$; 1.9%) and URTIs ($n = 3$). Table 2 lists the precipitating factors observed in the study. Other precipitating factors such as pollen inhalation, hepatitis, ingestion of naphthaline, co-trimoxazole and breast feeding, each accounted for only one case. In the single case of an infant who was admitted because of haemolysis secondary to breast feeding, the mother had ingested fava beans.

Table 3 lists the main haematological and biochemical parameters, with their mean values. The mean value for haemoglobin was 7.02 g/dL (4.37 mmol/L).

Of the whole studied sample, 50% were found to have severe anaemia, while only 1.2% of the patients did not suffer from anaemia (Table 4).

G6PD level was measured in 244 patients and found to be low in 228 patients (93.4%). The other 16 patients (6.6%) had a normal or high value.

It has been shown that after a haemolytic crisis, most of the patients were admitted to the hospital for three days (40.4%), and only one patient needed admission to the paediatric intensive care unit. Among the studied sample, 96.5% of the patients were effectively managed with blood transfusion. Among the studied sample, 69.4% of patients had a positive family history for haemolysis.

Figure 1 shows admissions by month. Most admissions of the studied subjects, secondary to haemolysis, were in April, March and May.

DISCUSSION

The Middle East is believed to have the world's highest overall frequency of the G6PD genetic defect, and this, in

Table 4 Status of anaemia among glucose-6-phosphate dehydrogenase-deficient paediatric patients

State of anaemia	*n* (%)
Severe anaemia (Hb <7 g/dL)	129 (50)
Moderate anaemia (Hb 7–10 g/dL)	120 (46.5)
Mild anaemia (Hb 10–11 g/dL)	6 (2.3)
Normal (Hb >11 g/dL)	3 (1.2)

Table 3 Mean values for haematological and biochemical parameters

Parameter	Mean value	Reference	Mean value (SI unit)	Reference (SI unit)
Haemoglobin	7.02 g/dL	11–13	4.37 mmol/L	6.84–8.09
Reticulocytes	7.36%	0.0–1.5		
Mean cell volume (MCV)	81.4 fL	80–90		
White blood cells (WBCs)	$14.6 \times 10^3/\mu L$	4.5–11	$14.6 \times 10^9/L$	4.5–11
Total bilirubin	4.2 mg/dL	Up to 1	71.82 μmol/L	Up to 17.1
Direct bilirubin	0.13 mg/dL	Up to 0.2	2.22 μmol/L	Up to 3.42
Glucose	5.6 mmol/L	4.2–6.4		
Urea	6.6 mmol/L	1.7–8.3		
Sodium	136.6 mEq/L	130–155	136.6 mmol/L	130–155
Potassium	4.25 mEq/L	3.5–5.3	4.25 mmol/L	3.5–5.3

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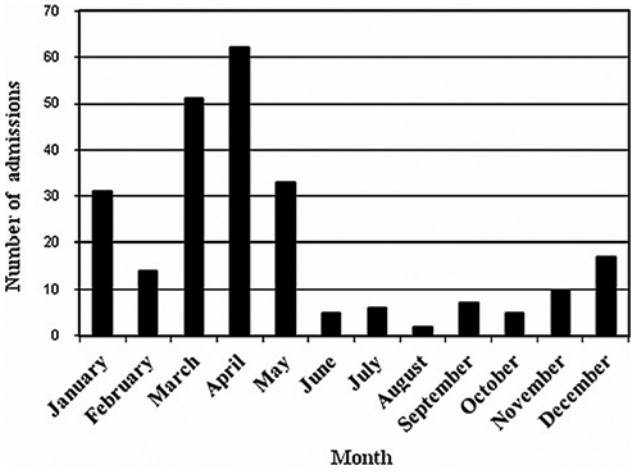

Figure 1 Number of admissions to hospital per month

addition to the region's unique geographical and historical features, makes it especially important and desirable to detect and characterize G6PD deficiency.[20]

Our results resemble those from Northern Sardinia,[19] in which ingestion of fava beans was the most common precipitating factor (94.4% of the sample) followed by the ingestion of drugs (2.5%) and viral hepatitis (0.1%).

It has been found that intrauterine haemolysis in G6PD-deficient fetuses exposed passively to fava beans is not common, in contrast to postnatal haemolysis through breast milk intake from mothers who ingested fava beans.[11] Results from our study, in which haemolysis was reported in a breastfed newborn whose mother had ingested fava beans, support this.

In our study, most of the cases of haemolysis were admitted in spring between March and May, supporting the causal relationship between fava bean ingestion and haemolytic episodes in G6PD-deficient individuals in Northern Jordan.

CONCLUSION

G6PD deficiency is an important health problem in Jordan and warrants greater attention from the medical community. We conclude that the most important precipitating factor for haemolysis in these patients was ingestion of fava beans. G6PD-deficient patients or their parents/care-givers must be counselled about avoiding trigger factors such as fava beans and certain other drugs, in order to minimize haemolysis crisis and to improve the patients' quality of life. Because there is no cure for favism, the best and simplest therapy is to avoid the trigger foods and behaviours, especially fava beans, and prohibited drugs. People with favism must also be sure to be vaccinated since infections can trigger an attack.

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