HKY Lau 劉潔如
CH Li 李澤荷
ACW Lee 李志偉

Acute massive haemolysis in children with glucose-6-phosphate dehydrogenase deficiency

葡萄糖-6-磷酸鹽脫氫酶缺乏症兒童出現急性大量溶血

We report seven consecutive episodes of acute massive haemolysis accompanied by symptomatic anaemia and gross haemoglobinuria in six boys with glucose-6-phosphate dehydrogenase deficiency seen in a regional hospital during a 12-year period. They presented at a mean age of 5.5 years (range, 1.5-11.3 years) with trough haemoglobin levels between 35 and 84 g/L. Two children developed transient renal impairment. Five children required erythrocyte transfusion, of whom one underwent exchange transfusion during the oliguric phase. Three patients required intensive care but all recovered from the haemolysis. The probable precipitating factors included consumption of fava beans (n=2), exposure to mothballs (n=1), treatment with herbal medicine or intramuscular injection of unknown nature (n=3), and upper respiratory tract infection (n=1). Although uncommon, acute massive haemolysis remains a life-threatening complication in children with glucose-6-phosphate dehydrogenase deficiency. Improvement in patient education and public health measures is suggested.

本文報告在一所分區醫院內，六名患葡萄糖-6-磷酸鹽脫氫酶缺乏症的男童在12年內共出現七次急性大量溶血，病發時都出現有症狀性貧血和大量血紅蛋白尿。這批男童平均年齡為5.5歲（介乎1.5-11.3歲），血紅蛋白濃度跌至極低水平，介乎35至84 g/L。2人出現短暫腎功能受損，5人接受紅細胞輸血，其中1人在少尿期要進行換血，3人要作重症護理，最後所有患者都康復。導致突然發作的原因包括誤吃蠶豆（n=2）、接觸樟腦丸（n=1）、接受草藥治療或不明藥物肌注（n=3），以及上呼吸道感染（n=1）。急性大量溶血雖然並不常見，但對患葡萄糖-6-磷酸鹽脫氫酶缺乏症的兒童來說，卻是可以致命的併發症，須加強對病人的教育和改善公共衛生的措施來加以防範。

Key words:
Favism;
Glucosephosphate dehydrogenase deficiency;
Hemolysis;
Naphthalenes;
Neonatal screening

關鍵詞：
蠶豆病；
葡萄糖磷酸鹽脫氫酶缺乏症；
溶血；
奈丸；
新生兒篩查

Hong Kong Med J 2006;12:149-51

Department of Paediatrics and Adolescent Medicine, Tuen Mun Hospital, Tuen Mun, Hong Kong
HKY Lau, FHKAM (Paediatrics)
CH Li, FHKAM (Paediatrics)
ACW Lee, FHKAM (Paediatrics)

Correspondence to: Dr ACW Lee (e-mail: aclee@graduate.hku.hk)

Introduction

Deficiency of glucose-6-phosphate dehydrogenase (G6PD), an X-linked recessive enzymatic defect in the hexose monophosphate shunt that protects cellular damage from oxidative stress, is a common haematological problem worldwide.[1] In Hong Kong, the prevalence of hemizygosity in males is 4.47% and that of homozygosity in females is 0.27%.[2] Patients who are G6PD-deficient are usually asymptomatic, but are susceptible to haemolysis after oxidative challenge.[1,3,4] Under overwhelming conditions, acute massive intravascular haemolysis may occur with abrupt onset of severe anaemia and gross haemoglobinuria. Acute renal failure is the most significant complication and can be lethal, although it rarely occurs in children.[4,5]

Deficiency of G6PD is the most significant factor that contributes to severe neonatal hyperbilirubinaemia and kernicterus,[6-8] thus universal neonatal screening for G6PD deficiency has been performed routinely in Hong Kong since 1984.[2] Cord blood samples from all newborn infants are sent to the Department of Health laboratory for measurement of G6PD enzymatic activity. Individual results are sent to the hospital where the baby was delivered. Parents of children diagnosed with G6PD deficiency receive written advice on substances and drugs that should be avoided and are offered counselling.

Table. Summary of the clinical and laboratory findings of acute massive haemolysis in this series

Patient No.	Age (years)	Haemoglobin (g/L)	Reticulocytes	Bilirubin (μmol/L)	Methaemoglobin	Admission to PICU*	Erythrocyte transfusion	Impaired renal function	Precipitating event/ chemical exposure
1[†]	11.3	71	6.7%	127	13.1%	Yes	Yes (5 units)	Yes (urea, 8.7 mmol/L)	Fava beans
2	2.5	55	5.8%	123	ND[‡]	No	Yes (1 unit)	No	Upper respiratory tract infection
3	1.8	35	6.2%	52	ND[‡]	Yes	Yes (1 unit)	Yes (urea, 13.2 mmol/L)	Mothballs
4	6.6	65	22.1%	95	4.1%	No	Yes (1 unit)	No	Herbal medicine containing Dolichos
5	5.8	65	19.2%	66	0.6%	No	No	No	Herbal medicine, nature not determined
	1.5	84	11.7%	25	ND[‡]	No	No	No	Unknown injection in Mainland China
6[§]	8.8	44	14.0%	119	3.5%	Yes	Yes (1 unit)	No	Fava beans

* PICU paediatric intensive care unit
† This patient received exchange transfusion during oliguria
‡ ND not done
§ This patient had not undergone neonatal screening; the haemolytic crisis was the first presentation of glucose-6-phosphate dehydrogenase deficiency

The local impact of G6PD deficiency beyond the neonatal period has not been systematically studied. The effect of the newborn screening programme on the health status of older children born in the last 20 years is likewise unknown. The present review of cases was carried out to address these issues.

Case series

Medical records of all patients admitted to the Department of Paediatrics of the Tuen Mun Hospital from March 1993 to February 2005, with a diagnosis of acute massive haemolysis and G6PD deficiency were retrospectively reviewed. Demographic data, clinical features, and laboratory findings were extracted. Acute massive haemolysis was defined as an abrupt onset of symptomatic anaemia, clinical jaundice, gross haemoglobinuria, and haematological features of haemolysis. The diagnosis of G6PD deficiency was made by reference, where applicable, to the neonatal screening programme of the Department of Health,[2] or by means of the fluorescence spot test[5] carried out in the hospital laboratory. Measurement of enzymatic activity and molecular diagnosis of the underlying genetic defect were not available. An attempt was also made to identify the precipitating cause in the 24-hour period preceding the onset of symptoms of haemolysis.

Six boys aged 1.5 to 11.3 years (mean, 5.5 years) presented with seven episodes of acute massive haemolysis. The patient who experienced two episodes of haemolytic crisis presented at the ages of 1.5 and 5.8 years. Five children, including a child of Pakistani origin, were born in Hong Kong and G6PD deficiency had been diagnosed in the neonatal period. None of them had serious or protracted jaundice during that time.

The clinical and laboratory findings are summarised in the Table. Erythrocyte transfusions were required in five instances because of compromised cardiorespiratory status. Three children required intensive care but all made a complete recovery. Exposure to fava beans or mothballs, substances that are notorious for causing haemolysis in cases of G6PD deficiency, was found in three (43%) cases. In the remaining patients, the immediate precipitating events included consumption of herbal medicine, receipt of an unidentified drug given intramuscularly in Mainland China, and an upper respiratory tract infection.

The parents of the five children in whom G6PD deficiency was diagnosed in the neonatal period had apparently forgotten the list of harmful substances that should be avoided. Patient 6 was born in Mainland China where universal neonatal screening is not available. Acute haemolysis was the first presentation of G6PD deficiency.

Discussion

Deficiency of G6PD is a disease of important health concern in Hong Kong, and since 1984 all newborn children have been subjected to universal screening.[2] The impact of the disorder on older children and adults has nonetheless not been systematically studied locally. Between 1962 and 1982, Chan[5] identified 14 male subjects with acute massive haemolysis associated with G6PD deficiency from the department of medicine of a tertiary teaching hospital. Only three (21%) patients were under the age of 15 years. Most patients had a concomitant diagnosis of infectious illness—upper respiratory tract infection (n=4), viral hepatitis (n=4), chronic active hepatitis and septicaemia (n=1), and typhoid (n=1). Drugs or chemicals were implicated in five cases—amidopyrine (n=1), Chinese proprietary medicine containing anti-inflammatory agent (n=1), and aniline dye (n=3). Four patients died from acute renal failure. To the best of our knowledge, no other local patient series is available for comparison.

As our department is the only facility that provides acute paediatric care for Tuen Mun and Yuen Long districts, and it is unlikely that an affected child would not seek medical attention, an estimation of the incidence of acute massive haemolysis associated with G6PD deficiency can be made. Based on a population of 92 475 male children under the age of 15 years in 2001,[9] and an estimated 4133 boys with G6PD deficiency, acute massive haemolysis affects 1.4 patients per 10 000 boys with G6PD deficiency per annum. As similar data are not available prior to 1984, it is impossible to tell if the implementation of universal newborn screening for G6PD deficiency has had any positive impact.

Almost half of the cases of acute haemolysis in this series were potentially avoidable. A waning of awareness with time after the initial diagnosis seems to be the most important factor. Repeated counselling and education at a primary care level for those affected may therefore be helpful. At a public health level, preventive measures may be useful. Subjects with G6PD deficiency may not even know what fava beans are until they collapse with favism.[10] A warning message about a possible harmful effect on G6PD-deficient subjects added to the package of products containing fava beans or naphthalene would help remind consumers who are at risk. Similar measures have been taken against foodstuffs or additives that contain phenylalanine in countries where phenylketonuria is prevalent (1 in 10 000 births).

In the two children who developed acute haemolysis after consuming herbal medicine in this case series, parents were unsure whether the traditional practitioners understood the implications of G6PD deficiency. With a few exceptions,[5] traditional Chinese medicine has not been studied meticulously with respect to G6PD deficiency. Given the popularity of traditional medicine and the prevalence of G6PD deficiency in Hong Kong, information on the risk and safety of herbal medicines is essential.

Children who were born in Mainland China from cross-border marriages and eventually move to Hong Kong are an area of concern. Accurate figures for such marriages are not available, but they have been estimated to be 15 000 per year.[11] Neonatal screening is not available in Mainland China and this group of G6PD-deficient children may be unaware of their vulnerability to oxidising drugs or chemicals. Clinicians should be aware of these facts when providing care to these children, and screening for G6PD deficiency should be considered part of a routine health assessment.

In conclusion, acute massive haemolysis is an infrequent but life-threatening complication in children with G6PD deficiency. Children identified by universal screening to be G6PD-deficient are still affected despite the provision of health care information to their parents at the time of birth. Additional measures are needed to translate the results of the screening programme into demonstrable benefits in the post-neonatal population.

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