Glucose-6-Phosphate Dehydrogenase Deficiency in an Old Woman

Antoine Briantais, Margaux Froidefond, Julie Seguier, Laure Swiader and Jean Marc Durand*

Departement of Internal Medicine, Aix-Marseille University, Hospital Timone, France

*Corresponding author: Durand Jean Marc, Professor, Departement of Internal Medicine, Aix-Marseille University, Hopital Timone 264 Rue Saint Pierre, 13385 Marseille cedex 05, France

Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common worldwide distributed hereditary red cells enzymatic defect, with a prevalence of 400 million affected subjects. It is a benign haematologic disorder, acute haemolytic crisis triggered by exposition to oxidative agents such as fava beans, drugs or infections might be its most common life-threatening clinical presentation. Although G6PD deficiency is X-linked recessive disorder, females are expected to have normal G6PD level. In Females heterozygous for X-linked recessive genes, an increased frequency of clinical manifestations might be expected with increasing age, due to G6PD activity related to the degree of skewing of X-inactivation. Caution in prescribing oxidative drugs in patients with glucose-6-phosphate dehydrogenase deficiency is generally observed due to the pro-hemolytic effect of these molecules. This precaution must also apply to the elderly woman.

Keywords

G6pd, Favism, X-Inactivation

Introduction

Glucose-6-phosphate (G6PD) deficiency is the most common human enzyme defect which affects more than an estimated 400 million people worldwide [1]. The most frequent clinical manifestations of G6PD deficiency are neonatal jaundice and acute hemolytic anemia, often triggered by oxidative stress from infection and exposure to medication and certain foods (e.g., fava beans) [1]. As G6PD deficiency is X-linked recessive disorder, females are expected to have normal G6PD levels. Deficient females are therefore either double heterozygotes or homozygotes for G6PD mutations. Here, we report a woman with heterozygote G6PD deficiency, who presented with a severe hemolytic anemia. We discuss the etiology of G6PD deficiency in females and emphasize the importance to consider G6PD deficiency in acute hemolytic anemia, not only in males, but also in females in relationship to the pattern of X-chromosome inactivation.

Case Report

A healthy 76-year-old woman was referred to our hospital for abdominal pain, fever 38 °C, jaundice and diarrhea after eating fava beans suggestive of G6PD deficiency. Her past health was normal. Physical examination showed tachycardia, anemic sclera, and mild jaundice. Complete blood count showed a picture of a hemolytic anemia (Hb 5.2 g/dL, MCV 101fl, reticulocytes 209 giga/l) with elevated LDH (764 U/L, normal 313-618 U/L) and total bilirubin (86 µmol/L, normal 0-21 µmol/L), and lowered haptoglobin (< 0.08 mg/dL, normal 26-185 mg/dL). The patient recovered after red blood cell transfusion. No further hemolytic episode occurred. No other causes of acute hemolysis were documented.

Spectrophotometric analysis revealed deficiency of G6PD (7.8 IU/g Hb hemoglobin, normal > 7.9/g hemoglobin). Indeed, a moderately decreased rate is usual in the acute phase of hemolysis because the rate is overvalued due to reticulocytes, cells richer in G6PD. A molecular typing showed the patient to be heterozygous for G6PD Mediterranean (nt 563 C > T point mutation), that is associated with acute hemolysis and favism. The percentage of skewing was 88%.

Discussion

In heterozygous females for the G6PD have, the mean red blood cell enzyme activity depends on the degree of inactivation of one of the X chromosomes and may be normal, mildly to moderate reduced, and grossly deficient [2]. In our female patient heterozygous for G6PD Mediterranean, the genetic defect was silent until...
she was 76-year-old, when she developed her first hemolytic crisis following fava beans ingestion. According to the report of Au, et al., who showed that an increase of G6PD deficiency due to skewing occurred mostly in women older than 70 years [2], our patient had never had a hemolysis flare during previous consumption of beans. This fact could be likely attributed to an unbalanced X-chromosome inactivation pattern arising gradually in life and predominantly affecting the X-chromosome carrying the normal G6PD gene. The amount of skewing increases with age, so that 70-90% of females older than 70 years showed significantly skewed X-inactivation [3]. Therefore, in females heterozygous for X-linked recessive genes, an increased frequency of clinical manifestations might be expected with increasing age, due to G6PD activity related to the degree of skewing of X-inactivation.

Au, et al. [4] reported 18 heterozygotes women for G6PD mutation out of 173 old-women at a median age of 90 years (range: 80-107 years). A G6PD deficiency was observed in 1.73% of cases (three patients). This frequency of G6PD deficiency was significantly higher than that of 0.27% in female newborns. There were varying degrees of skewing of X-chromosome inactivation for the whole cohort, ranging from 0% to 73% (median: 44%). In G6PD-deficient heterozygotes, the skewing appeared to be toward the X-chromosome bearing the wild-type allele as in heterozygotes with normal G6PD activities, the skewing was toward the X-chromosome with the mutant allele.

In populations with prevalent G6PD mutations, the prescription of drugs with oxidizing properties to male patients will often be preceded by a biochemical assay for G6PD. In contrast, such a precaution is rarely taken when the patients are women, as the double heterozygosity and homozygosity frequencies for G6PD mutations are presumed to be very low [1]. Although this presumption may work in young women, the same may not be true in elderly women, where skewing of X-chromosome inactivation may occur, leading potentially to clinical manifestations of X-linked recessive genetic diseases.

With the high frequency of G6PD mutations in many populations [1] and increasing longevity, potential heterozygous elderly women at risk of age-related G6PD deficiency are numerous, constituting a worldwide health problem. Therefore, it might be prudent to screen for G6PD activity before prescribing oxidative drugs to elderly females.

Conflict of Interest
The authors have no conflict of interests to disclose.

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Contributions
We declare an equal contribution of the authors to the writing of case report. All listed authors concur in the submission and are responsible for its content; they have agreed to its publication and have given the corresponding author the authority to act on their behalf in all matters pertaining to publication.

References