First episode of acute hemolysis due to G6PD deficiency in a middle-aged woman and transmission of the enzymatic defect through bone marrow transplant

Haematologica 2004; 89:(1)e11

G6PD deficiency is a common erythrocyte enzymatic disorder characterized by clinical, biochemical and molecular heterogeneity, being point mutations the most frequently detected genetic defect. Because the G6PD gene is located on the X chromosome, the clinical manifestations of the disease are usually confined to hemizygous men.[1] However, female carriers might also have hemolytic anemia in relationship to the pattern of X-chromosome inactivation.

We report on a female patient from the Po valley area who developed favism for the first time at the age of 54. Past medical history revealed a colecistectomy. In 1998, at the age of 50, she underwent bone marrow harvest for her brother affected with CML. At that time, blood counts were normal and no biochemical abnormalities were detected. In June 2002, following fava beans ingestion she developed a clinical picture consistent with acute hemolysis with jaundice, hemoglobinuria, fever and back pain. Hb fell to 6.5 g/dL, total bilirubin level was 10.9 mg/dL (unconjugated 7.38 mg/dL), LDH level was 2969 mU/mL, aptoglobin level was undetectable; WBC count was $13x10^9$/L with normal differential count. In the past, she had already ingested fava beans without haemolytic crisis. The patient recovered spontaneously and one month later peripheral blood counts were normal (Hb 13.1 g/dl, RBC $4.010x10^9$/L, with moderate reticulocytosis). Erythrocyte G6DP activity was 90 mU/10^9 Erytr. (n.v. 118-144) and 2.71 UI/gHb at the spectrophotometric method (n.v. 6.01±1.1 UI/gHb) at two evaluations performed during the recovery phase. No other causes of acute hemolysis were documented (Coombs test negative, PNH clone absent, glycerol test negative). A molecular typing showed the patient to be heterozygous for G6PD Mediterranean (nt 563 C>T point mutation), that is the most common variant in Italy[2] and is associated with acute hemolysis and favism. The other members of her family (parents, three sisters and the brother) had never suffered from acute or chronic hemolytic anemia. The X-chromosome inactivation pattern was established by analysis of DNA methylation at the human androgen receptor (HUMARA) as previously reported.[3] A markedly skewed X-inactivation was revealed in the patient's neutrophils but not in T lymphocytes. Patient's brother was tested for G6PD deficiency and showed decreased erythocytic enzymatic activity (65 mU/10^9Erythr.). G6PD activity level before transplant was not available. He had normal blood counts and displayed a complete chimerism with a 46XX karyotype on bone marrow cells. HUMARA assay revealed the same unbalanced X-inactivation pattern as observed in his sister. Since transplant procedure he has never suffered from haemolytic anemia despite heavy and prolonged exposure to multiple drug.

First attack of favism usually affects homozygous males in their childhood and is relatively rare in adults. In our female patient heterozygous for G6PD Mediterranean, the genetic defect was silent until her middle age, when she developed her first haemolytic crisis following fava beans ingestion. 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. It is known, indeed, that an acquired pattern of skewed X-inactivation is detectable in 15% of 25-35-year-old healthy women and in 30 to 50% of women older than 60, in neutrophils more than in T lymphocytes.[3,4] It is also possible that acquired skewing, occurring as an age-related stochastic event, worsened a constitutional (genetic) X-inactivation defect,[5] thus promoting disease manifestation. This event has already been reported in other X-linked hematopoietic disorders.[6] At the time of writing, the patient is well with normal blood counts. Nevertheless, tacking into account that a clonal myeloid malignancy has occurred in her brother, clinical follow-up is indicated to check for the emergence of a true clonal hemopoiesis.

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Contributions and Acknowledgments
EO , ML and MV were involved in clinical assessment of patients and drafting the article. GB performed clonality studies. All the Authors contributed to the interpretation of the data and revised the manuscript . The Authros gratefully acknowledge MD Cappellini Maria D., Centro Anemie Congenite, IRCCS Ospedale maggiore Policlinico, Padiglione Granelli, Dipartimento di Medicina Interna, Università degli Studi di Milano, Italy, for molecular typing of G6PD DNA.

Disclosures: Redundant publication: no substantial overlapping with previous papers

Conflict of interests: none

References

1. Beutler E. G6PD population genetics and clinical manifestations. Blood Rev 1996; 10: 41-52
2. Martinez di Montemuros F, Dotti C, Tavazzi D, Fiorelli G, Cappellini MD. Molecular heterogeneity of glucose-6-phosphate dehydrogenase (G6PD) variants in Italy. Haematologica 1997; 82: 440-445.
3. Tonon L, Bergamaschi G, Dellavecchia C, Rosti V, Lucotti C, Malabarba L et al. Unbalanced X-chromosome inactivation in haemopoietic cells from normal women. Br J Haematol 1998; 102: 996-1003.
4. Busque L, Mio R, Mattioli J, Brais E, Blais N, Lalonde Y et al. Nonradom X-inactivation patterns in normal females: lyonization ratios vary with age. Blood 1996; 88:59-65
5. Puck J, Willard HF. X inactivation in females with X-linked disease. N Eng J Med 1998; 338: 325-328.
6. Cazzola M, May A, Bergamaschi G, Cerani P, Rosti V, Bishop DF. Familial-skewed X-chromosome inactivation as a predisposing factor for late-onset X-linked sieroblastic anemia in carrier females. Blood 2000; 96:4363-4365.