Bleeding symptoms in heterozygous factor VIII deficiency

Whether or not heterozygous carriers of partial deficiencies of rare coagulation defects exhibit a bleeding tendency is an open issue.[1,2] This issue is critical for our understanding of the need (or lack of need) for replacement therapy when these patients undergo surgery or other invasive procedures. Recently in this journal Ivaskevicius *et al.*,[3] in their elegant description of several mutations of the gene encoding the factor XIII A submit, report that 8 of their 12 heterozygous patients, with plasma factor XIII levels ranging from 23% to 71%, had bleeding symptoms at the time of provocative events such as trauma, dental extractions, parturition or surgery. Spontaneous bleeding in mucosal tracts (menorrhagia, unspecified mucosal bleeding) is also reported.[3] As a result of their findings, the authors recommend carrying out a quantitative assay of factor XIII activity in people referred because of a positive clinical history of post-operative bleeding.[3] I believe that this recommendation is premature on the basis of the evidence presented in the publication. It is well established that significant bleeding symptoms may occur also in normal people,[4,5] and none were included as controls in the study of Ivaskevicius *et al.*[3] Moreover, the evidence gained by observing the relationship between the occurrence of bleeding symptoms and the levels of factor XIII attained in homozygotes kept prophylactically on regular replacement therapy indicates that trough plasma levels as low as 3% to 10% are sufficient to keep these severely affected patients free from bleeding.[6] Bleeding symptoms in people with levels of factor XIII higher than 10% have only been reported in the frame of a questionnaire survey[7] that had inherent limits in terms of an accurate correlation between clinical manifestations and laboratory phenotype. The findings of Ivaskevicius *et al.*[3] and others[1,2] also emphasize the need to develop a score specific for patients with rare coagulation disorders, which should help to draw a more precise line between bleeders and non-bleeders.

Pier Mannuccio Mannucci

Scientific Direction and A. Bianchi Bonomi Hemophilia and Thrombosis Center, IRCCS Cà Granda Foundation Maggiore Hospital, Italy

Key words: factor VIII, blood coagulation.

Correspondence: Pier Mannuccio Mannucci, via Pace 9, 20122 Milano, Italy; Phone: +39 02 55035421; Fax: +39 02 50320723; Email: piermannuccio.mannucci@unimi.it or pmmannucci@libero.it

Citation: Pier Mannuccio Mannucci. Bleeding symptoms in heterozygous factor VIII deficiency. Haematologica 2010;95:e6

doi:10.3324/haematol.2010.028969

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