A Genetic View on the Etiology of the Inhibitor Complication

To the Editor:

The ever-increasing prospects of replacement therapy of inherited diseases by gene transfer turn the spotlight more than ever onto the causes of the inhibitor complication in the hemophilias. We feel, therefore, that a few comments on the role of the hemophilia mutations and the manner in which the influence of different factors could be dissected will not go amiss.

The nature of the hemophilia mutation is, of course, an etiologic factor easy to single out, but the others, genetic or environmental, are probably multifarious and partly unknown. Definitive evidence of the importance of the hemophilia mutations has accumulated since 1983. In hemophilia A, 37% of patients with gross deletions (26/71), 30% of those with frameshifts and nonsense mutations (28/94), and 20% of those with large inversions have inhibitors (130/642), whereas only 3.1% (2/64) of patients with similarly severe disease caused by missense mutations, single amino acid deletions, and other in-frame small deletions or duplications have the complication.1,2

In hemophilia B, the incidence of inhibitors is lower than in hemophilia A, but the same correlation exists between mutation type and risk of inhibitors. Thus, in the UK and world lists, respectively, 12% (8/65) and 11% (28/248) of patients with gross deletions, nonsense, and frameshift mutations have inhibitors, versus 0% (0/113) and 0.46% (2/433) of those with the missense and other mutations causing severe hemophilia, i.e., a disease characterized by factor IX activity between 0% and 2% of normal (Green et al, unpublished results).3,4

The many-fold difference in the frequency of the inhibitor complication between the patients with the two major groups of mutations mentioned above strongly suggests that the predisposing effect of the hemophilia mutation may be related to the failure to produce sufficiently normal FVIII or FIX because this failure is most unlikely in the low risk group of mutants. Interestingly, different nonsense mutations in the FVIII gene seem associated with different risks of the inhibitor complication and the consequences of nonsense mutations may sometimes be alleviated by exon skipping. Thus, of the five nonsense mutations detected by Naylor et al,5 three (codon 1696, 1874, and 1966) did not alter mRNA splicing, whereas two (codon 1987 and 2116) were accompanied by skipping that prevented protein truncation and led simply to FVIII missing, respectively, the amino acids of exon 19 or 22. Consequently, the former three nonsense mutations cause a much greater loss of coding information than the latter. Correspondingly, only one of the seven patients with any of the first three nonsense codons has no inhibitors, whereas none of the six with the latter two mutations has the complication.6 This may still be mere coincidence, but the whole body of data leaves no room for doubting the role of the hemophilia mutations.

The next task is to dissect and determine the role of the other factors in the etiology of the inhibitor complication. It is logical therefore to ask whether the combined effect of all genetic factors is significant once the hemophilia mutation has been accounted for. This can be performed by determining how, with regard to the inhibitor complication, the concordance between pairs of relatives varies as the degree of their blood relationship decreases. Because genetic factors other than the hemophilia alleles are not likely to be closely linked to the FVIII or FIX locus, the concordance between pairs of relatives should significantly decrease with increasing distance of the blood relationship. Using this approach, information from families with different mutations can be pooled. Once the role of the combined factors has been assessed, subsets such as genes in the major histocompatibility complex can be tested.

Environmental factors may also influence the concordance between pairs of relatives. To distinguish between genetic and specific environmental factors and investigate the effects of the latter, a series of pairs of relatives with similar environmental experience should be compared with an equivalent series of pairs with dissimilar environmental experiences. If the environmental factors studied are important, pairs of relatives in the second series will show lower concordance. Among the environmental factors, the nature of the coagulant preparations has been the object of recent discussion. Of course, an intriguing question is whether leakage of maternal blood in the fetal circulation may exercise a protective effect. If this were so, perinatal replacement treatment of individuals at risk would be indicated.

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REFERENCES


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