Why should hemophilia B be milder than hemophilia A?

We read with interest the report by Melchiorre *et al.*[1] on the milder clinical parameters in hemophilia B as compared to hemophilia A.

The single most important factor which contributes to the severity of hemophilia is the nature of mutations. Even the phenotypically severe hemophilia cases can further be subclassified based on the type of mutations they carry i.e., null mutations like inversions and gross deletions which result in the total absence of factors against non-null mutations like missense, nonsense or single base pair deletions or insertions, where some residual factor is being synthesized which however will not be detected in the conventional one stage factor assays. However, this type of classification may not always stand true, for instance, some of the missense or nonsense mutations can result in a phenotype similar to the null mutations, depending on their location or the functional implications of that region.[2]

There is a differential distribution of mutations in relation to their severity in hemophilia A and B. About 40-50% of severe hemophilia patients are positive for intron 1 and 22 inversion mutations resulting in the total absence of the residual FVIII protein. Even after excluding the inversions, both HA and HB mutation databases show that less severe gene defects are more common in HB than in HA.[3,4]

For an appropriate comparison of the clinical phenotype between hemophilia A and B, one should correlate the null mutations *versus* the non-null mutations in both hemophilia A and B, which will provide a more appropriate answer as to whether there are any differences between the type of factor deficiency and the severity of the disease.

Shrimati Shetty[1] and Kanjaksha Ghosh[2]

[1]National Institute of Immunohaematology (ICMR), 13th floor, KEM Hospital, Parel, Mumbai; and [2]Surat Raktadan Kendra & Research Centre, Udhana, Surat, Gujarat 394210, India

Correspondence: shrimatishetty@yahoo.com

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