Mutation Type Dependent Inhibitor Risk – a Single Center Study on 432 Patients with Severe Hemophilia A

J. Oldenburg, J. Schröder, R. Schwaab, C. Müller-Reible, E. Seifried, P. Hanfland, and H.-H. Brackmann

Alloantibodies (inhibitors) against factor VIII (FVIII) in Hemophilia A represent a major complication in patient care because they render classical substitution therapy ineffected. Inhibitors occur at a frequency of 20-30 %. Herein we report on 432 patients with severe hemophilia A, known mutation with the FVIII gene and known inhibitor status representing the largest cohort ever been reported from a single center (Bonn). The underlying mutation was correlated to the inhibitor prevalence as well as to the inhibitor titer.

From the 432 patients, 205 (47,45 %) hemophiliacs showed the prevalent intron-22-inversion, 8 (1.85 %) the intron-1-inversion, 61 (14.12 %) a nonsense mutation, 65 (15.05 %) a small deletion/insertion, 61 (14.12 %) a missense mutation, 17 (3.94 %) a large deletion and 15 (3.47 %) a splice site mutation. 79 (18.29 %) of the 432 patients developed an inhibitor of which 46 (58 %) showed a high titer and 33 (42 %) a low titer. Inhibitor prevalences for the main mutation types were 35.29 % in large deletions, 25 % in intron-1-inversion, 21.46 % in intron-22-inversion, 21.31 % in nonsense mutations, 13.85 % in small deletions/insertions, 13.33 % in splice site mutations and 4.92 % in missense mutations. However, for mutations subtypes inhibitor prevalences could be as high as 100 % (3 out of 3) in multi domain large deletions and as low as 0 % (0 our of 16) in small deletions/insertion affecting an adenine series.

Although for some mutation types the numbers are still small the results corresponding well to those reported earlier on merged patient samples and underline the significant influence of the mutation type to the risk of inhibitor formation.

I. Scharrer/W. Schramm (Ed.)
35th Hemophilia Symposium Hamburg 2004