
Universiteit
Leiden
The Netherlands

Three problems of hemophilia B : a study of abnormal factor IX molecules with an inhibitor neutralization assay

Briët, E.

Citation
Briët, E. (1977, June 16). *Three problems of hemophilia B : a study of abnormal factor IX molecules with an inhibitor neutralization assay*. Drukkerij "Luctor et emergo", Leiden. Retrieved from https://hdl.handle.net/1887/61512

Version:	Not Applicable (or Unknown)
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/61512

Note: To cite this publication please use the final published version (if applicable).

Cover Page

Universiteit Leiden

Leiden University Repository

The handle http://hdl.handle.net/1887/61512 holds various files of this Leiden University dissertation

Author: Briët, Ernest
Title: Three problems of hemophilia B : a study of abnormal factor IX molecules with an inhibitor neutralization assay
Date: 1977-06-16

THREE PROBLEMS OF HEMOPHILIA B

a study of abnormal factor IX molecules
with an inhibitor neutralization assay

THREE PROBLEMS OF HEMOPHILIA B

a study of abnormal factor IX molecules
with an inhibitor neutralization assay

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE AAN DE RIJKSUNIVERSITEIT TE LEIDEN, OP GEZAG VAN DE RECTOR MAGNIFICUS DR. D. J. KUENEN, HOOGLERAAR IN DE FACULTEIT DER WISKUNDE EN NATUURWETENSCHAPPEN, VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN TE VERDEDIGEN OP DONDERDAG 16 JUNI 1977 TE KLOKKE 14.15 UUR

door

ERNEST BRIËT
geboren te Voorst in 1945

1977

DRUKKERIJ „LUCTOR ET EMERGO" — LEIDEN

PROMOTOR:

Dr. J. J. VELTKAMP

CO-REFERENTEN:

Dr. W. HIJMANS

Prof. Dr. J. J. SIXMA

Financial support was obtained from the "Hippocrates Studiefonds".

CONTENTS

INTRODUCTION

Hemophilia is a sex linked, recessive, hereditary disorder characterized by excessive bleeding. This bleeding tendency manifests itself in spontaneous hemorrhages in the joint cavities and muscles, and in excessive bleeding after trauma or surgical procedures.

The first written references to the disease can be found in the Babylonian Talmud, in which it can be read that Rabbi Judah the Patriarch exempted the third son from circumcision if his mother had already lost two sons because they had bled to death after this operation (1). Rabbi Simon ben Gamaliel even forbade a boy to be circumcised when sons of his mother's three elder sisters had died from bleeding after circumcision (2).

In the 19th century Wardrop discovered the prolonged clotting time of hemophilic blood. For a long time lack of prothrombin was held responsible for the clotting defect until in 1935 Quick found that the prothrombin time of hemophilic plasma was normal (2).

Patek and Taylor reported in 1937 that the prolonged clotting time of hemophilic plasma could be normalized by the addition of a globulin fraction of normal blood. For this reason the lacking clotting component was called antihemophilic globulin; later, by international agreement, it was named clotting factor VIII (2).

In 1944 Pavlovsky observed that a mixture of the blood of two hemophiliacs known to him had a normal clotting time (3, 4). The right interpretation of this finding was given only in 1952 and not by Pavlovsky himself. In that year reports from New York, San Francisco, and Oxford described a disease which was clinically and genetically undistinguishable from hemophilia, but the lacking clotting component was not factor VIII (5-7). The missing factor in this new disorder, PTC-deficiency, Christmas disease or hemophilia B, was later called factor IX.

Hemophilia is a relatively rare disorder with an incidence of approximately 1: 10,000 men if mild cases are also taken into

account. Some 15% of hemophiliacs suffer from hemophilia B (8). The disease frequently causes severe destruction of joints with much suffering and disability to the patients. The economic burden for society that pays for the lifelong and costly treatment of the patients is very heavy. As a consequence, one endeavours all over the world in this field of the medical sciences to prevent irreversible damage to joints or even to prevent the disease altogether by means of genetic counseling of carriers.

In this thesis three aspects of hemophilia B are discussed. The first concerns the heterogeneity of hemophilia B. Some patients with hemophilia B have biologically inactive factor IX molecules in their plasma. These molecules show a cross-reaction with antibodies against normal factor IX. Because of this property these patients are classified as B^+ or CRM-positive. The question as to whether patients lacking factor IX molecules completely, B^- or CRM-negative patients, really exist, or whether absence of factor IX molecules is due to the imperfection of laboratory techniques, is a matter of debate to which we shall add our view. The second problem concerns the detection of carriers of hemophilia B. Carrier detection is an important issue for the female relatives of a hemophilic patient because they have a chance of bearing sons with this potentially disabling disease. In a large proportion of possible carriers it is difficult to ascertain whether such a woman is a carrier or not. We shall describe our attempts to improve carrier detection. Furthermore we studied the in vivo yield of factor IX concentrates. When factor IX concentrates are transfused into patients with hemophilia B for the treatment or prophylaxis of bleeding, a considerable proportion of the transfused factor IX molecules is not recovered in the plasma compartment of the patient. We report the progress of our search for these lost factor IX molecules.

The inhibitor neutralization assay (INA), which is applied for the assay of factor IX-CRM, has been extensively used by several authors who described molecular variants of factor IX. Its application in carrier detection has been reported twice (9, 10), whereas, to our knowledge, it has never been used in the study of factor IX concentrates. Apart from the factor IX activity assay, the INA forms the methodological mainstay of this study. A description of this test is given in Chapter I.

REFERENCES

1. Rosner, F.: Hemophilia in the Talmud and rabbinic writings. Ann. Intern. Med. *70:* 833-837, 1969.
2. Ingram, G. I. C.: The history of haemophilia. J. Clin. Pathol. *29:* 469-479, 1976.
3. Castex, M. R., Pavlovsky, A., Simonetti, C.: Contriboción al estudio de la fisiopatogenia de lau hemofilia. Med. B. Aires 5: 16-34, 1944.
4. Pavlovsky, A.: Contribution to pathogenesis of hemophilia. Blood *2:* 185-191, 1947.
5. Schulman, I., Smith, C. H.: Hemorrhagic disease in an infant due to deficiency of a previously undescribed clotting factor. Blood *7:* 794-807, 1952.
6. Aggeler, P. M., White, S. G., Glendening, M. B., Page, E. W., Leake, T. B., Bates, G.: Plasma thromboplastin component (PTC) deficiency: a new disease resembling hemophilia. Proc. Soc. Exp. Biol. Med. *79:* 692-694, 1952.
7. Biggs, R., Douglas, A. S., Macfarlane, R. G., Dacie, J. V., Pitney, W. R., Merskey, C., O'Brien, J. R.: Christmas disease. A condition previously mistaken for haemophilia. Brit. Med. J. *II:* 1378-1382, 1952.
8. Veltkamp, J. J., Schrijver, G., Willeumier, W., Putte, B. van de, Dijck, H. van: Hemophilia in the Netherlands. Results of a survey on the medical, genetic and social situation of the Dutch hemophiliacs. Acta Med. Scand. *S572:* 3-24, 1974.
9. Elödi, S.: Factor IX activity and factor IX antigen in haemophilia B carriers. Thrombos. Res. *6:* 39-51, 1975.
10. Matsuoka, M., Ito, M., Takahashi, K., Sakuragawa, N.: An immunological method for detection of the carrier of hemophilia B. Thrombos. Haemostas. *36:* 441-450, 1976.