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A NEW TREATMENT FOR VON WILLEBRAND'S SYNDROME

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It is generally accepted that the lack of synthesis of various coagulation factors is the cause of different types of congenital hemorrhagic diatheses. Exceptions occur in the case of circulating anticoagulants, but these are very rare.

Although bleeding episodes can be fairly well controlled in the different kinds of coagulation disorders by the administration of appropriate plasma and plasma fractions, the ideal treatment for an inborn error of metabolism is to increase the synthesis of the deficient factor.

Recently, we reported the case of a patient with congenital afibrinogenemia in whom the fibrinogen level was raised to low normal values by the administration of Lyndiol^{R}, with no side effects. Under treatment with this oral contraceptive, the patient had two teeth extracted without undue bleeding.[1,2]

In this preliminary communication, we are reporting the successful results of Lyndiol^{R} treatment in a patient with von Willebrand's syndrome who has had AHG deficiency in addition to prolonged bleeding time and abnormal platelet adhesivity. Oral contraceptives have also been given to 21 other patients with different kinds of hemophilia. The results of this treatment will be reported separately.

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Case Report

M. I. (63/22808), an eleven year old boy, was first seen at Hacettepe Children's Hospital at the age of eight years with a history of epistaxis and prolonged bleeding from cuts. His first bleeding episode occurred during the neonatal period with bleeding from the cord stump. He was circumcised at the age of two years and bleeding continued for 20 to 25 days. Frequent nose bleeds were noted beginning at the age of four. After he started to walk, his parents noted large areas of ecchymosis on his lower extremities following minor traumas. There appeared to have been no bleeding into the joints, however.

The patient's parents are not related and none of the other siblings (a girl and three boys) has a history of bleeding. The parents stated, however, that both the maternal grandfather and great-grandfather had marked bleeding tendencies. We could not confirm this as neither of these men was living.

Physical examination : The patient was a well-developed preadolescent boy with a few areas of ecchymosis on his legs. A grade I/IV systolic murmur was heard in the precordial area. The liver and spleen were not palpable. Other than several decayed teeth, the rest of the examination was not remarkable, and the blood pressure was 115/70 mmHg.

Laboratory examination : Hemoglobin, 12.3 gm per 100 ml; WBC, 5600 per cmm with a normal differential count; platelet number and morphology appeared normal on peripheral smear. Urinalysis and liver function tests were normal. The results of coagulation studies are given in the table. There was no fibrinolysis and no circulating anticoagulants could be demonstrated. Screening test for Factor XIII gave normal results.

Following blood bank plasma transfusion (10 cc per Kg) his bleeding time dropped to 2.5 minutes, and was not over five minutes 18 hours after transfusion. However, 20 hours later bleeding time increased to more than 25 minutes. His six deciduous decayed teeth were extracted under fresh frozen plasma transfusions, which were continued over a period of seven days.

The patient was given oestrogen tablets (five mg per day) for five weeks, and tests were then done to determine the effect of this hormone on bleeding time and Factor VIII (AHG) level. During this period, neither the AHG level nor TGT changed, but bleeding time was six minutes in the third and fourth weeks. In the fifth week of treatment, however, bleeding time increased to 20 minutes.

Treatment was continued with Lyndiol R* (lynestrenol, 2.5 mg and methoxyethinyloestradiol, 0.075 mg), one tablet per day, and coagulation studies, including Quick prothrombin time, Factor II, V, VII - X, fibrinogen, TGT and AHG assays and bleeding time determinations, were repeated every three weeks. Although some improvement in TGT was observed after three weeks of treatment, the AHG level did not change even after five months of treatment. However, after eight months, AHG activity did increase up to 24 per cent and TGT was found completely normal with patient's adsorbed plasma. Platelet adhe-

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* Lyndiol was kindly supplied by Mr. Konuralp Başol, from the Organon Drug Company.

TABLE

RESULTS OF COAGULATION STUDIES OF THE PATIENT

Tests	Patient	Normal
Bleeding time Ivy, A. C., Shapiro, P. R. and Melnick, P.: Surg., Gynec, and Obstet. 60 : 781, 1935.	22.5'	8.0'
Tourniquet test	negative	negative
Platelet count Rees-Ecker method Enumeration of Platelets, Cartwright, G.E., ed., Diagnostic Laboratory Hemotology, third edition, New York, London, Grune and Stratton, 1963, p. 77.	188,000	150,000-400,000
Quick prothrombin time Quick, A. J.: J. Biol. Chem. 109 : 73, 1935.	13"	13"
Fibrinogen Ratnoff, O. S. and Menzie, C.: J. Lab. Clin. Med. 37 : 316, 1951.	332 mg %	250-400 mg %
Platelet adhesivity Modified Borchgrevink's method Acta Med. Scand. 163 : 157, 1960.	0 %	40 % (minimum)
Antihemophilic globulin level McMillan, C. W., Diamond, L. K. and Surgenor, D. M.: New Engl. J. Med. 265 : 221, 1961.	0.5 %	50-200 %
Factor XIII Josso, F., Prou-Wartelle, O., Alagille, D. and Soulier, J. P.: Nouv. Rev. Frans d'Hemat. 4 : 267, 1964.	(+)	(+)

Thromboplastin generation test (TGT)
Biggs, R. and Douglas, A. S.: J. Clin. Path. 6 : 23, 1953.
(minimal substrate clotting time is recorded)

	Normal adsorbed plasma and normal serum	Patient's adsorbed plasma and normal serum	Normal adsorbed plasma and patient's serum	Patient's adsorbed plasma and serum
Initial	11.9	23.9	12.1	25.5
8th mo. of treatment	11.7	11.5	11.9	11.9

sivity did not show any improvement during the treatment period. Bleeding time also decreased in the first nine weeks to two minutes, but the decrease was not maintained constantly and after four months of treatment, bleeding time was 20 minutes. Although there were some other changes in coagulation factors, these were not constant either.

The patient is still being treated with Lyndiol[R] and, except for gynecomastia, there have been no side effects.

Discussion

In von Willebrand's syndrome (or vascular hemophilia) there is usually a deficiency of AHG in addition to prolonged bleeding time. Deficiencies in Factor IX (PTC)[3] and Factor XI (PTA)[4] have only rarely been reported. Platelet adhesivity tests seem to be more reliable in the diagnosis of this condition than bleeding time.[5]

Although a deficiency of platelet Factor III has been shown in only a few cases, the existance of this association merits confirmation.[6,7] Bleeding time can be shortened in patients with this syndrome by administration of plasma, obtained either from normal donors or from hemophilia patients. The increase in Factor VIII thus obtained may persist for up to 40 hours.[8,9] Platelet adhesivity can be corrected by administering normal plasma.[10] The ATP/ADP ratio is also found to be increased in the platelet-rich plasma of patients with this disorder.[11]

Classical hemophilia (Factor VIII deficiency) and Christmas disease (Factor IX deficiency) are sex-linked diseases, and for this reason generally occur in males. Von Willebrand's syndrome is inherited as an autosomal dominant character with variable expressivity.[5] For this reason, if the lack of a thromboplastic factor is observed in a female, the possibility of vascular hemophilia should be considered before circulating anticoagulants or chromosomal sex abnormalities.

In the present case, the diagnosis of von Willebrand's syndrome was determined by the prolonged bleeding time, decreased platelet adhesiveness and Factor VIII deficiency. The diagnosis was further confirmed by the fact that bleeding time could be corrected by administration of normal plasma.

Congenital deficiencies of different kinds of coagulation factors are molecular diseases. The generally accepted treatment for these conditions is the administration of appropriate plasma or plasma fractions at intervals determined by the *in vivo* half-life of the fraction, and during bleeding episodes or surgery.

In 1962 it was demonstrated for the first time that AHG levels could be raised by administering corticosteroids to patients with classical hemophilia.[12] Corticosteroids cannot be used continuously in high doses because of the harmful side effects, therefore another medicine had to be found that could safely be used to stimulate the synthesis of AHG. The value of Episilon-amino caproic acid therapy in hemophilia is still under discussion. However, even in those cases where some beneficial effects have been obtained, AHG activity has not been raised.[13–16]

It has been noted that AHG levels are well below 30 per cent in some female carriers without any manifestations.[17] It has also been reported that the activity level of several coagulation factors, including Factor VIII, increases during pregnancy in normal persons, as well as in patients with von Willebrand's disease.[18–20] In «pseudopregnancy» caused by oral contraceptives, it can be shown that several coagulation factors can be raised in normal persons,[21, 22] Factor VIII level in suspected carriers of hemophilia A,[23] and Factor X activity in persons with this factor deficiency.[24] As stated above, the fibrinogen level was significantly augmented in one of our patients with congenital afibrinogenemia.[1, 2] With these facts in mind, we successfully used Lyndiol^{R} in the treatment of the patient described here. This patient has had no bleeding episodes while under Lyndiol^{R} treatment, in spite of some trauma.

Although the patient's AHG half-life was not measured (because lack of synthesis of this factor is characteristic of von Willebrand's syndrome), we believe that Lyndiol^{R} increases the synthesis of Factor VIII. It is well established that when AHG activity is raised by plasma transfusion in cases of vascular hemophilia, bleeding time decreases. In spite of a fairly high AHG level, the defect in our patient's platelet adhesivity was not corrected. This may indicate that some other factor in addition to AHG is involved in platelet adhesivity. Bleeding time varies to a certain extent in patients with von Willebrand's syndrome, and may even vary from time to time in the same patient. We were able to bring about a decrease in our patient's bleeding time in the course of two months of treatment, even though there was no change in Factor VIII level. However, the decrease in bleeding time could not be maintained and eventually it rose to over 20 minutes, were it remained despite the augmentation of AHG level. These facts suggest that in this disorder, bleeding time is not strictly related to Factor VIII levels either.

Since the effect of oestradiol on *in vivo* platelet adhesivity in vascular hemophilia had been reported,[25] we used oestrogen tablets (5 mg per day) in the treatment of our patient for five weeks. The drug had only a temporary effect on the reduction of bleeding time, and furthermore, the dosage required caused marked gynecomastia. During the period of treatment with Lyndiol^{R} (eight months) no major side effects [26] other than moderate gynecomastia and marked growth acceleration were observed. Because this treatment appears to effect a basic correction of an inborn error of metabolism, we will continue to use it in treating these types of disorders.

Summary

The case of a patient with von Willebrand's syndrome successfully treated with Lyndiol^{R} (one tablet per day) is presented. The patient's AHG level was increased from 0.5 per cent to 24 per cent during eight months of therapy. A temporary decrease in bleeding time occurred without any accompanying increase in Factor VIII at the beginning of treatment. Platelet adhesivity could not be corrected. No major side effects of the drug have been observed other than moderate gynecomastia and marked growth acceleration.

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