Willebrand factor in von Willebrand's disease

The diagnosis of von Willebrand's disease (VWD) is usually made from the prolonged bleeding times and reduced plasma clotting factor VIII (F VIII C) activities of persons with a positive family history. The characteristically prolonged rise in F VIII C after plasma or cryoprecipitate treatment confirms the diagnosis. Recent discoveries have shown reduced levels of antigenic factor VIII (F VIII Ag) and diminished glass-adhesion induced and ristocetin induced aggregation of platelets in VWD plasma. All these defects are corrected in vitro and in vivo by fractions of normal plasma which are closely linked to F VIII Ag. These fractions contain "(von) Willebrand factor" (F VIII W.F.), whose concentration is very low in VWD plasma and which can be assayed using its ability to cause platelets to aggregate with ristocetin—a phenomenon of pharmacological rather than physiological significance. The existence of atypical families indicates that there may be several "molecular" variants—for example, some with normal F VIII Ag but low F VIII W.F.

Kernoff et al. found that factor VIII treatment to VWD patients was followed by a persistent rise of high-molecular weight F VIII Ag and F VIII C. On the other hand, Bennett et al. found that whereas such treatment was followed by persistently high F VIII C activity, the F VIII Ag levels fell rapidly; and Bloom et al. noted a parallel rapid fall of F VIII W.F. activity and lengthening of the bleeding time. Stapleforth et al. suggest that this pattern indicates that the infused F VIII Ag is consumed during the synthesis of the new F VIII C. We have observed the levels of F VIII C, F VIII Ag, and F VIII W.F. (Meyer's washed platelet system) in two patients with classical VWD after cryoprecipitate treatment.

Case reports

Case 1.—A 16-year-old girl had 10 packs during a severe nosebleed. Though the F VIII C level remained raised at first, that of F VIII Ag and F VIII W.F. both declined rapidly to their former levels with a half-life of about 10 hours. Her bleeding time (Ivy's method) was four and a half minutes immediately after infusion, but over 13 minutes 22 hours later.

Case 2.—A 36-year-old woman presented with an acute and distressing dental abscess. Her F VIII W.F. was 28%, and F VIII Ag 63% of pooled normal plasma, and her F VIII C was 0.45 U/ml. Her tooth was extracted and left to drain. Initial cover with eight packs of cryoprecipitate was insufficient for haemostasis and another 12 packs were required four hours later. Bleeding stopped promptly. Twenty-six hours later her F VIII Ag level was falling, but her F VIII C and F VIII W.F. levels were still quite high (see table). One month later levels were much lower, showing that at presentation she was synthesizing additional materials sufficient to increase by about 25%, above the basal levels of active F VIII W.F., F VIII Ag, and F VIII C. Active synthesis may well have been continuing during the period under study making any analysis of the rates of decay unreliable.

Discussion

These contrasting responses illustrate the desirability of "basal" conditions when carrying out such studies. Moreover, they do not necessarily support the idea that persons with some varieties of VWD can synthesize F VIII Ag and F VIII W.F. after treatment, whereas others cannot. Synthesis of F VIII W.F. under stress might explain the observations of Kernoff et al. and also the frequently observed rapid haemostasis of many patients with VWD in acute surgery—for example, appendicitis—in spite of lack of factor VIII cover. We would expect the spontaneous remissions observed in pregnancy to be accompanied by synthesis of F VIII W.F.; and possibly the homozygous patients of Stapleforth et al. failed to remit because of the lack of sufficient synthesis. Reduced but detectable synthesis by VWD heterozygotes may occur under conditions known to increase F VIII C and F VIII Ag levels in normal persons.

Sinus bradycardia following treatment with hyd ergine for cerebrovascular insufficiency

The use of Hyd ergine (dihydroergotoxine mesylate) in the treatment of patients suffering from dementia as a result of cerebrovascular insufficiency has been the subject of recent reports. Studies of drugs used in treating dementia using the automated pair matching test included the action of Hyd ergine in a few patients with dementia resulting from cerebrovascular disease (multi-infarction dementia). In a small trial in which Hyd ergine was given to eight patients three developed a serious degree of sinus bradycardia associated with a general deterioration in their condition necessitating ending the treatment.

Case Reports

Case 1.—A woman aged 85 presented with a five-year history of organic dementia with symptoms and signs suggesting cerebrovascular aetiology. Her cardiovascular system was clinically normal, blood pressure 135/80 mm Hg, pulse 70-80 beats/min sinus rhythm; the electrocardiogram (ECG) showed evidence of old inferior infarction. She was treated with Hyd ergine 1-5 mg three times a day for seven days and at the end of this time developed a sinus bradycardia of 40 beats/min with evident general deterioration in her condition.

Case 2.—A 69-year-old man had a two-year history of dementia with signs and symptoms showing a cerebrovascular aetiology. The cardiovascular system was normal, blood pressure 150/95 mm Hg, ECG normal and also the frequently observed rapid haemostasis of many patients with VWD in acute surgery—for example, appendicitis—in spite of lack of factor VIII cover. We would expect the spontaneous remissions observed in pregnancy to be accompanied by synthesis of F VIII W.F.; and possibly the homozygous patients of Stapleforth et al. failed to remit because of the lack of sufficient synthesis. Reduced but detectable synthesis by VWD heterozygotes may occur under conditions known to increase F VIII C and F VIII Ag levels in normal persons.


Department of Haematology, The London Hospital Medical College, London E1 2AD
F E BOULTON, MD, MRCPATH, Senior Lecturer (Present address: Department of Haematology, University of Liverpool, Liverpool L69 3BX)
M J LLOYD, FIMLT, Senior Technologist
An ECG confirmed the presence of sinus bradycardia in all three patients; the deterioration in their general health consisted of withdrawal, listlessness, refusal of food, and general apathy. The pulse reverted to normal and the symptoms disappeared within two days of ending the drug.

Discussion

Hydrogine contains 1·5 mg of mesylates of dihydrogenated alkalioids of dihydroergokryptine. The substance is thought to have a profound alpha-blocking action. It has also been suggested that it may have beta-adrenergic blocking effects. 4 The bradycardiac effect of Hydrogin is mentioned in earlier European literature particularly in relation to the use of Hydrogin in peripheral vascular disease, but we have been unable to find a mention in the more recent literature in this country referring to its use in cerebrovascular insufficiency. Further research into the action of Hydrogin on the heart rate would be of interest. We feel the development of this complication in three out of eight patients treated with Hydrogin associated with severe systemic symptoms is of sufficient importance to report these cases.

We thank Mrs J Newman, SRN, and Mrs P Southward, SRN, for helping with the running of the trial.

1. Rehman, S A, Current Medical Research and Opinion, 1973, 1, 8.

Department of Geriatrics, Middlesex Hospital, London WIN 8AA
A C DCAYLEY, MB, MRCP, senior registrar
A MACPHERSON, MB, MRCP, research assistant
J WEDGWOOD, MD, FRCP, consultant in geriatric medicine

SLE precipitated by antibodies in a patient with Sjögren's syndrome and rheumatoid arthritis

Typical rheumatoid arthritis and systemic lupus erythematosus (SLE) are often considered as separate diseases with different prognoses and treatments. Sjögren's syndrome has been reported in association with both diseases. 1 It has been suggested, however, that SLE and rheumatoid arthritis may well represent opposite ends of a spectrum of connective tissue diseases and that overlap cases combining features of both diseases may occur. 2 This latter concept is illustrated by the patient reported here, in whom a disease with the typical, clinical, and serological features of SLE was precipitated by antibodies on two occasions but who had otherwise typical rheumatoid arthritis with Sjögren's syndrome in the intervening period.

Case History

Mrs AB, aged 42 in April 1973, developed polyarthralgia, fever and a chest infection two weeks after treatment for a sore throat with a 12 day course of co-trimoxazole. She had a history of respiratory tuberculosis treated with chemotherapy in 1961, while her mother had had Sjögren's syndrome and rheumatoid arthritis. After further treatment elsewhere with co-trimoxazole and rifampicin, ethambutol, and isoniazid she became ill with worsening of her polyarthralgia and pericarditis. LE cells were seen in the blood film; the titre of serum antinuclear factor was 1/1000, and that of rheumatoid factor 1/256, while DNA binding 28%, (borderline abnormal). SLE was diagnosed, all therapy stopped, and high dose prednisolone started. She improved clinically and steroids were tailed off. During follow-up over the next year at the Centre for Rheumatic Diseases she developed symptomatic Sjögren's syndrome with typical ocular and oral manifestations. She continued to have intermittent peripheral joint pain and stiffness and developed synovial hypertrophy of the metacarpophalangeal and proximal interphalangeal joints of the hands and x-ray changes of periarthritis osteoporosis and juxta-articular erosions.

She was managed with non-steroidal anti-inflammatory drugs and by December 1974 her serum antinuclear factor had become negative, DNA binding 0%, and the titre of rheumatoid factor 1/1025. She remained generally well otherwise until April 1975, when she was again treated with co-trimoxazole at home for a sore throat. After this she remained generally unwell for a month until she was admitted to hospital in May with fever and signs of a left basal pneumonia. She was then treated with co-trimoxazole initially and rapidly became worse with confusion, pyrexia, and extreme weakness. Laboratory tests showed DNA binding of 60%, with an anti-nuclear factor titre of 1/1000, complement C3 160% (normal 75-150%), complement C4 60% (normal 31-55%). Co-trimoxazole was stopped and she was again treated with high dose steroids and improved clinically in parallel with a change in her abnormal serological indices.

Discussion

This patient developed the multi-system features of SLE on two occasions after the administration of antibiotics, including co-trimoxazole. Sulphonamides, like penicillin, have been reported to precipitate SLE in those predisposed, 3 and it seems likely that they, rather than the trimethoprin component of co-trimoxazole, were responsible in this case. Antibodies to native DNA 4 were demonstrated during this patient's second illness and, as they are not usually found in drug-induced SLE, their presence in the patient may represent true SLE activated in a susceptible patient by drugs.

This case history emphasises the care that must be taken in considering giving antibiotics not only to patients with a previous history of SLE but also to those known to have Sjögren's syndrome. It also supports the present concept that SLE and rheumatoid arthritis exist as different poles of a spectrum of disorders, with patients with Sjögren's disease perhaps occupying an intermediate position. We think that further studies of patients like ours with similar overlap syndromes might give a greater understanding of the various disease processes concerned.


The Centre for Rheumatic Diseases and University Department of Medicine, Royal Infirmary, Glasgow

D M GRENNAN, MB, MRCP, medical registrar
G BELL, MB, CHB, house officer
P J ROONEY, MB, MRCP, senior medical registrar
A G KENNEDY, MB, MRCP, senior medical doctor

Acute rhabdomyolysis and acute renal failure after intravenous self-administration of peanut oil

Nontraumatic rhabdomyolysis with myoglobinuria may cause acute renal failure (ARF). Several agents may initiate rhabdomyolysis and another one is protected.

Case Report

A 27-year-old labourer was admitted to hospital unconscious. During the preceding 12 hours he had taken alcohol, cannabis, nitrazepam, Palfium (dextromoramide), and cocaine in unknown quantities and methadone by intravenous injection. In addition he had injected into his veins the contents of ten Hemineurin capsules. Each capsule contained 192 mg of chloramphenicol base and 384 mg of peanut oil. He was drowsy and complained of severe pain in the lower back and legs. The thighs and buttocks were appreciably swollen, painful, and tense, and there was a flaccid paraplegia with loss of pain and tactile sensation below L2 with sacral sparing. Vibration sense was absent in the legs.