Spectrum of hereditary coagulation factor deficiencies in Eastern Province, Saudi Arabia

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SUMMARY In a 7-year retrospective analysis (1991–97) of the records of the Department of Haematology, Regional Laboratory and Blood Bank (Dammam), 54 patients from all parts of Saudi Arabia's Eastern Province were diagnosed with hereditary coagulation factor deficiencies. The largest group of patients, 42 haemophiliacs, included 4 non-Saudi patients. There were 39 haemophilia A or factor VIII deficiency patients, 2 haemophilia B or factor IX deficiency patients and 1 combined factor VIII and V deficiency patient. There were 5 Saudi patients with probable factor XIII deficiency, and 7 patients, all but one who were Saudi, had von Willebrand disease. The distribution of haemophilia patients in Eastern Province showed some differences compared with those reported from Riyadh and from Western countries. Among Saudis in Eastern Province, the number with suspected factor XIII deficiency, although low, was higher than that reported for other regions. The number of patients with haemophilia B and von Willebrand disease was lower than expected, when compared with the number of haemophilia A cases.

Introduction

Hereditary coagulation factor deficiencies (HCFD) have been reported from all parts of the world. Haemophilia and von Willebrand disease (vWD) are the most common types of hereditary factor deficiencies. Other types are much rarer [*1*]. The incidence of haemophilia does not seem to vary between different geographic areas or ethnic groups [*2*]; vWD, on the other hand, does [*3*]. The severity of the resulting bleeding tendency and the pattern of bleeding varies between the different types of factor deficiency. Some may only cause a mild bleeding tendency, while others can cause lifelong severe bleeding problems [*1*]. In our retrospective study we present our experience in Eastern Province Saudi Arabia, and attempt to better understand the prevalence of HCFD in this part of the world.

Patients and methods

Of the 54 patients whose records we reviewed, all had documented bleeding episodes. Approximately 67% (36 patients) were followed up locally. The rest were referred to us for diagnostic analysis only. Of these, some were initially screened in their respective hospitals, then referred to us to complete the analysis, confirm diagnosis and advise on management.

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All patients had complete blood count (Sysmex NE 8000, Toa Corporation, Japan) and blood smear examination. Blood for coagulation assays was collected in 1/10 volume of 3.8% trisodium citrate. Platelet-poor plasma was separated within 1 hour by centrifugation at 2000 g for 15 minutes. Single-stage prothrombin time (PT), activated partial thromboplastin time (APTT) and thrombin time (TT) assays were carried out using an Amelung KC10 coagulometer (Amelung, Germany). Fibrinogen was estimated by a modified von Clauss method. Fibrin/fibrinogen degradation products (FDPs) were estimated by latex agglutination, using commercial reagents from various sources. Correction studies for PT and APTT, and the Bethesda assay for factor VIII inhibitor were performed using standard methods and pools of normal plasma, obtained from 10–20 normal subjects. Factor XIII screening was performed using clot solubility in 5 mol/L urea. Clotting factor assays were performed by single-stage assay using an Amelung KC10 coagulometer (Amelung, Germany), commercial factor deficient plasma and calibration standards from various sources.

For vWD, we used standardized template bleeding time (Simplate R, Organon Tecknika Corporation, United States of America), ristocetin cofactor assay (vWF-RiCoF) (Biopool, United States of America), and platelet aggregation response to ristocetin. The last two assays were performed on Bio/Data PAP-4 platelet aggregation profiler (Bio/Data Corporation, United States of America). The von Willebrand factor antigen (vWF-Ag) was assayed using Asserachrom vWF enzyme immunoassay kit (Diagnostica Stago, France). Cross immunoelectrophoresis, platelet glycoprotein analysis and vWF multimer assay were unavailable to us. We used standard criteria for diagnosis of haemophilia and vWD [*2–4*].

Results

A total of 54 patients fulfilled the criteria for HCFD. Only 5 patients were non-Saudis. Table 1 shows the distribution.

Haemophilia

Haemophiliacs, the largest group, totalled 42 patients. The 39 patients (3 non-Saudis) with factor VIII deficiency (haemophilia A) included only 1 female. There were 2 patients (1 non-Saudi) with factor IX deficiency (haemophilia B). A Saudi male patient had combined factor VIII and V deficiencies.

Clinical severity varied widely among the patients with factor VIII deficiency (Table 2). As expected, there was a general correlation between clinical severity and patients' baseline factor VIII:C levels [*2*]. All patients received factor VIII concentrate on demand, and none received home treatment. There were 9 Saudi patients (1 female) who had severe disease with spontaneous soft tissue haematoma and haemarthrosis. They had a mean factor VIII:C of < 1.0% (normal range 50%–200%). There were 3 families with more than one family member who were patients. A patient who had been infected with human immunodeficiency virus (HIV) by contaminated factor VIII concentrate (one of two patients), later died from AIDS-induced illness. A brother and sister, and one other patient, developed inhibitors. The brother and sister both had weak inhibitors of < 10 Bethesda units (BU), (normal < 0.6 BU), and both inhibitors were poorly inducible when challenged with human factor VIII. The other patient was a brisk responder, with a very strong inhibitor (> 400 BU), responding only to porcine factor VIII concentrate. He was later treated with recombinant factor VIIa (rF-VIIa) and his inhibitor is now fading.

Table 1 **Distribution of patients with hereditary coagulation factor deficiencies**

Diagnosis	No. of families	No. of patients	Sex (M/F)	Nationality (Saudi/non-Saudi)
Factor VIII deficiency	32	39	38/1	36/3
Factor IX deficiency	2	2	2/0	1/1
Factor VIII and V deficiency	1	1	1/0	1/0
Factor XIII deficiency	?3	5	2/3	5/0
Von Willebrand disease				
Type I	4	4	3/1	3/1
Type II	3	3	1/2	3/0
Total	46	54	47/7	49/5

Table 2 **Distribution of patients with haemophilia according to clinical severity**

Clinical severity	No. of patients[a]	Mean factor VIII:C (%)[b]	Range factor VIII:C (%)	Nationality (Saudi/non-Saudi)
Severe	9	<1.00	–	9/0
Moderate	13	3.65	2–6	11/2
Mild	16	12.38	5–38	15/1

[a]One case (preterm baby) with undetermined clinical severity is not included.
[b]Normal factor VIII:C = 50%–200%

Interestingly, one of the patients with factor VIII deficiency was a female from a known family of haemophiliacs. She had mental retardation, and chromosomal study revealed her to be an XX-female with ring chromosome 9. This explained her mental retardation but did not explain her low factor VIII level. She had one severely affected older brother. Her other two brothers, two sisters and mother had normal factor VIII levels. The cause of her affliction was presumed to be an example of extreme inactivation of her normal X chromosome [*1*]. She had a mild disease at first, but like her brother developed a weak inhibitor of < 10 BU. She now has moderately severe disease, and is still responsive to high-dose human factor VIII concentrate treatment.

There were 13 male patients who had moderate disease, of whom 2 were non-Saudi. They suffered from post-traumatic haematoma and occasional haemarthrosis. Mean factor VIII:C was 3.65%, range 2%–6%. There were 16 male patients with mild disease (1 non-Saudi), who suffered post-traumatic haematoma and prolonged bleeding after dental extraction. Mean factor VIII:C was 12.38%, range 5%–38%. They had normal bleeding time and RiCoF levels. Among the 16 patients with mild disease was 1 who was HIV-positive, and 2 patients from one family with known disease. The clinical severity of one of these siblings, a preterm baby (30 weeks gestation), with factor VIII:C level of 1.0% at birth, has not as yet been determined.

The patient with combined factor VIII and V deficiencies, or familial multiple coagulation factor deficiencies type 1 (FMFD-1), was a Saudi male child with only mild disease. He presented with prolonged postdental extraction bleeding. Both PT and APTT were repeatedly prolonged, with factor VIII:C of 23% and factor V of 40% (normal range 50%–200%). He had normal bleeding time and RiCoF level. This patient received factor VIII concentrate for his bleeding episode. Desmopressin (DDAVP), when available, together with fibrinolytic inhibitors, would have been a more useful substitute for controlling his mild postdental extraction bleeding.

Two male patients had factor IX deficiency. They both received factor IX concentrate on demand, or were alternatively treated with fresh frozen plasma (FFP) infusions when the latter was not available. One patient, a Saudi boy diagnosed at age 2 years, had severe disease and baseline factor IX levels of 1.0% (normal range 40%–160%). He suffered from post-traumatic haematoma formation and occasional haemarthrosis. The second patient was a middle-aged Pakistani man with moderate disease. He had baseline factor IX levels of 5.0%. He suffered from occasional post-traumatic bleeding and soft tissue haematoma.

Factor XIII deficiency

There were 5 patients with probable factor XIII deficiency, all of whom were Saudi, and 3 female. Diagnosis was based on the results of screening tests and clinical picture (confirmatory tests are unavailable in the country). They presented with prolonged bleeding from post-dental extraction and cuts. Typically, the bleeding was delayed for 12–36 hours, and some reported poor wound healing. The females also had a history of menorrhagia. Of the 2 male patients, one had had a bleeding diathesis since infancy, while the other was an infant who had a fatal postcircumcision haemorrhage. The diagnosis in the latter case was made in retrospect, during the post-mortem investigation that followed the patient's death. A family study for this case could not be arranged as the family were too distressed and were ultimately lost to follow-up. All our patients had a clear defective solubility in 5 mol/L urea, but with normal PT, APTT, fibrinogen and FDP levels, and normal bleeding time.

von Willebrand disease

There were 7 patients (3 females, 4 males) diagnosed with vWD (Table 3), of whom all but one were Saudi. The non-Saudi patient was a female infant with moderately severe disease. The only non-Saudi patient, plus 3 others, had quantitative deficiency or type I disease. The other 3 of the 7 patients had probable type II disease.

Type I disease patients had prolonged template bleeding time and a mean vWF-RiCoF of 22.0%, range 20%–24% (normal 50%–200%). All except one had absent platelet response to ristocetin at 0.25–1.25 mg/mL (normal response is seen between 0.63 mg/mL and 1.25 mg/mL). The exception was one who had absent response at 0.25–1.0 mg/mL and reduced response at 1.25 mg/mL. Among the type 2 patients, two had moderate to severe bleeding tendency, with low factor VIII:C of 2.0% and 3.0% respectively (normal 50%–200%). The other 2 suffered only from post-traumatic bleeding. Their factor VIII:C was 23.0% and 50.0% respectively. The severity of the bleeding tendency in this group seemed to correlate well with low factor VIII:C level.

There were 3 patients who had probable qualitative deficiency, or type II disease, including one type IIb. All had mild bleeding

tendency with only post-traumatic bleeding, and prolonged template bleeding time and normal factor VIII:C. Two had a clear discrepancy between low vWF-RiCoF level and high vWF-Ag level (a ratio of 1.6 and 2.1). The female patient with type IIb had menorrhagia, occasional purpuric rash and episodic thrombocytopenia with platelet counts between 70 × 10^9/L and 150 × 10^9/L (normal 150–450 × 10^9/L). She had prolonged bleeding time, vWF-RiCoF 152.0%, factor VIII:C 70.0% and manifested an increased platelet aggregation response to ristocetin at 0.25 mg/mL and 0.5 mg/mL (normal response 0.63–1.25 mg/mL).

Discussion

The results of our study show some correlation with those previously reported by Ahmed et al. from Eastern Province [5], namely rarity of factor IX deficiency in comparison with factor VIII deficiency. This differs from the experience reported by Al-Fawaz et al. from Riyadh [*6*]. An experience we did share with Al-Fawaz et al. was that vWD was the second most common HCFD.

Haemophilia A and B are inherited X-linked haemorrhagic diseases. Their incidences, 1/10 000 and 1/25 000–1/30 000 male births respectively, do not seem to vary between different geographic areas or ethnic groups [*2*]. The ratio of Saudi patients with haemophilia A to haemophilia B in our group of patients from Eastern Province was 36:1, much higher than the expected ratio of 3:1. Although family studies were incomplete for some of our patients, the reasons behind this higher than expected ratio is unclear (even if some patients were to turn out to be distantly related). Further studies from other regions in the country are required to illuminate the discrepancy. The majority of our patients had mild to moderate severity, similar to the reports of Al-Fawaz et al. [*6*]. This is in contrast to the results of Awidi in Jordan, where there was a higher proportion of clinically severe cases [*7*].

The patient with FMFD-1 had factor VIII:C of 23% and factor V of 40%. Because of the wide difference between factor VIII and V levels, both of which share a 40% common core structure, we suspect this to be a coincidental coexistence of two gene defects, rather than a defective common gene [*8*]. The family study has still to be carried out.

Searching for female carriers during family studies and genetic counselling is not easy because of the overlap between factor VIII levels of normal and carrier females. The use of recombinant DNA techniques not only allows the identification of the different mutations in a given population, but also makes detection of carrier females much easier. Recently, many medical geneticists, molecular biologists and biochemists worldwide have been increasingly turning their attention to this subject. This is amply illustrated by the inclusion of 472 factor VIII mutations in the haemophilia A database [*9,10*], and 637 factor IX mutations in the haemophilia B database [*10,11*].

Our study seems to have identified a group of patients with probable factor XIII deficiency not hitherto reported in Saudi Arabia. Factor XIII deficiency is a very rare autosomal recessive hereditary bleeding disorder, with consanguineous marriage very common among the parents of such patients [*12*]. Confirmation of the diagnosis in this group is necessary, as cases of deficiency of alpha-2-antiplasmin and tissue plasminogen activator inhibitor type I (tPAI-I) may give defective solubility in 5 mol/L urea. Similarly, structurally abnor-

Table 3 **Details of patients with von Willebrand disease**

Type of bleeding	Sex/ nationality	Platelet count (150–450 × 10^9/L)	Template bleeding time (< 9.0 minutes)	(Factor VIII:C (50%–200%)	vWF-RICoF (50%–200%)	vWF-Ag (50%–200%)	Ristocetin aggregation (0.63–1.25 mg/mL)	Family history	Type of vWD and clinical severity
Joints and mucous membrane from infancy	F/non-Saudi	Normal	Prolonged	Low at 2.0%	Low at 20.0%	Not available	Absent	Negative severe	Type 1 moderately
Postdental extraction	F/Saudi	Normal	Prolonged	Normal	Low at 42.0%	Normal at 90.0% ratio 2.1	Normal	Negative	Type II mild
Postdental extraction	M/Saudi	Normal	Borderline	Low at 3.0%	Low at 24.0%	Low at 25.0%	Reduced at 1.25 mg/mL, absent at 0.25–10 mg/mL	Negative	Type mild
Heavy periods and skin	F/Saudi	Episodic 70–150 × 10^9/L	Prolonged	Normal	Normal at 152.0%	Not available	Increased response at 0.25–0.5 mg/mL	Positive	Type IIb mild
Postdental extraction and mucous membrane	M/Saudi	Normal	Borderline	Low at 3.0%	Low at 21.0%	Not available	Absent	Negative	Type I moderate
Postdental extraction	M/Saudi	Normal	Borderline	Normal	Borderline 50.0%	Normal at 80.0% ratio 1.6	Normal	Positive	Type II mild
Soft tissue and mucous membrane	M/Saudi	Normal	Prolonged	Normal	Low at 23.0%	Low at 39.0%	Absent	Positive mild	Type I

Normal ranges are given in brackets. vWF-RiCoF = ristocetin cofactor assay vWF-Ag = von Willebrand factor antigen

mal fibrinogen may also give defective solubility in 5 mol/L urea. These conditions are usually accompanied with abnormal fibrinogen, reptilase time and FDP assays, which was not the case in our group. Here, too, the situation is similar to that of haemophilia. The search for heterozygous carriers in the family requires more sensitive tests than those used for screening and would benefit from DNA techniques [*13*].

It is to be noted that four of our patients came from the Al-Ahssa area, including two females and an infant who suffered a fatal postcircumcision haemorrhage. At least three are thought to belong to the same extended family. However, proving this to be the case is difficult because of a lack of civil records going back any length of time. In factor VIII deficiency, there is deficiency of the factor in both platelets and plasma, and since this factor is responsible for the cross-linking of fibrin monomers and for stabilization of the fibrin clot, patients usually have a history of lifelong bleeding diathesis from early infancy, poor wound healing and repeated abortions in females [*12*]. Central nervous system bleeding is also a common complication in this disease [*12*]. Treatment is by FFP infusions. Factor XIII concentrate is also available (not in Saudi Arabia). Prophylactic treatment is also effective because of the long half-life of factor XIII.

The second most common HCFD in our study was vWD. The confirmation of the diagnosis in type II disease requires analysis of the multimeric structure of vWF in plasma and platelets and platelet membrane glycoprotein analysis [*3,4*]. These are time-consuming and complicated procedures requiring a certain level of expertise and specialized laboratories, unfortunately not available to us. Availability of many primers for the more common types of vWD will make DNA-PCR (polymerase chain reaction) analysis an extremely useful technique in both the definitive diagnosis of vWD and in family studies.

vWD is characterized by a variable mode of inheritance, depending on the exact subtype [*4*]. Affected individuals usually have a lifelong bleeding tendency. Clinical severity of the disease again depends on the vWD subtype, but mucocutaneous bleeding is the most common symptom seen in patients with vWD [*4*]. Post-traumatic bleeding, especially after dental extraction, is common. Postpartum and postoperative bleeding can be severe unless the patient is properly prepared for surgery. The choice of treatment in any given patient depends upon the severity of the disease, the type of vWD, the factor VIII:C level and the clinical setting, but cryoprecipitate is the preferred blood product for replacement therapy [*3*]. FFP can also be used, but it is a less satisfactory alternative. Both products suffer from similar drawbacks, mainly the risk of transmission of infection. DDAVP together with fibrinolytic inhibitors are very useful in dealing with postdental extraction bleeding [*3*].

The overall prevalence of vWD in European countries and North America varies from as low as 3–4/100 000 for the autosomal dominant, severe form of the disease, to as high as 1/100 for mild forms of the disease [*3*]. The reason for the low number of vWD in Eastern Province, in comparison with the number of haemophilia cases, remains to be determined.

Whether multimeric analysis of vWF would have been useful in reclassifying some of the mild haemophiliacs as vWD is an open question. We also believe that some patients with mild disease are being missed, although this may change with the increase in clinical awareness among physicians, and with the introduction of more sensitive DNA techniques.

If we are to unravel the true picture of HCFD in our part of the world, regional facilities for the diagnosis of hereditary bleeding disorders need to be upgraded. We must also find ways of overcoming the reluctance of families to undergo screening tests for logistic reasons as well for fear of stigma. We hope that our study will add to the limited information available on the prevalence of hereditary bleeding disorders in Saudi Arabia, as well as in other countries of the Middle East.

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