Peer reviewed article

Congenital hypersensitivity to vitamin K antagonists due to FIX propeptide mutation at locus -10: a (not so) rare cause of bleeding under oral anticoagulant therapy in Switzerland

Silvia Ulrich[a], *Brigitte Brand*[a], *Rudolf Speich*[a], *Johannes Oldenburg*[b], *Lars Asmis*[a]

[a] Departments of Internal Medicine, University Hospital of Zurich, Zurich, Switzerland
[b] Institute of Experimental Haematology and Transfusion Medicine, University Hospital of Bonn, Bonn, Germany

Summary

Question under study: In most countries hypersensitivity to vitamin K antagonists (VKA) is considered to be a rare congenital bleeding diathesis. It occurs in patients with FIX propeptide mutations at locus -10.

Patients, method and results: We present a Swiss family with two patients who suffered major bleedings under oral anticoagulant treatment in the presence of therapeutic or subtherapeutic INR levels and abnormally prolonged aPTT. In both patients a mutation in the propeptide of FIX at locus -10 with substitution of alanine by threonine (Ala-10Thr) was found. In one patient FIX clotting activity was found to be severely reduced (2%). The observed bleeding tendency is related to this – compared to the other vitamin K dependent factors (FII, FVII, FX) – excessively and disproportionately low level of FIX. Three generations of this family were tested for propeptide mutations, which are transmitted in an X-chromosomal recessive mode of inheritance. Apart from the two symptomatic male patients we found another male with the mutation who has not been exposed to VKA, six female carriers and four potential male carriers in the fourth generation who have not been tested. A founder effect for this mutation has been previously described for cases in Switzerland and Germany.

Conclusion: FIX propeptide mutation-associated hypersensitivity to VKA is a rare occurrence in Switzerland. The severity of associated bleeding complications and the reversible nature of the bleeding diathesis may nonetheless warrant increased awareness on the part of primary care physicians in Switzerland.

Key words: Factor IX gene; oral anticoagulation; bleeding; coumarin sensitivity

Introduction

Oral anticoagulant therapy (OAT) with vitamin K antagonists (VKA) is indicated for the prevention and treatment of arterial and venous thromboembolism [1]. Due to inter-individual variability of vitamin K intake, vitamin K resorption, vitamin K metabolism and metabolic pathways relevant for the synthesis and posttranslational modification of coagulation factors, clinical response to OAT is highly variable. OAT thus requires individualised dosing regimes and drug monitoring. A highly relevant adverse drug effect of OAT is so-called "major bleeding". Major bleeding is frequently defined as bleeding that is intracranial or retroperitoneal or necessitates

List of abbreviations

Ala	Alanine
Glu	Glutamine
F	Coagulation factor
FIX PM	Factor IX propeptide mutation
INR	International normalised ratio
OAT	Oral anticoagulant therapy
Thr	Threonine
VKA	Vitamin K antagonists
VKA-HS	Vitamin K antagonist hypersensitivity
aPTT	Activated partial thromboplastin time

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transfusion, requires hospitalisation and/or leads to death. Its incidence varies according to the definition that is adopted, the indication for OAT, the intensity of OAT and the length of therapy. In anticoagulated patients the reported incidence of major bleeding is 1–7 patients/100 patient years or 1–7% (fatal bleeding approximately 0.5%) [2].

Vitamin K antagonists inhibit coagulation by limiting the availability of biologically active vitamin K through inhibition of hepatic γ-carboxylase, an enzyme involved in posttranslational modification of coagulation factors which is necessary for biological function. This enzyme's activity requires biologically active vitamin K as an obligatory cofactor. Anticoagulation with VKA thus leads to reduced bioavailability of vitamin K and reduced posttranslational modification of vitamin K-dependent coagulation factors. The latter results in an altered three-dimensional structure of vitamin K-dependent coagulation factors (FII, FVII, FIX and FX). The more rigid three-dimensional conformation of these non-carboxylated coagulation factors is associated with inhibited coagulation through their reduced capacity to bind to and interact with activated surfaces [3–6].

In rare instances OAT-related bleeding is associated with a mutation of the factor IX (FIX) gene. Two propeptide mutations have been described at locus -10: Ala(GCC)-10Val(GTC) and Ala(GCC)-10Thr(ACC) [7, 8]. The propeptide sequence at locus -10 plays an important role in the anticoagulant effect of VKA, since it contains the binding site for hepatic γ-carboxylase [9]. In the presence of a mutation at the propeptide locus -10, the binding of hepatic γ-carboxylase to the FIX protein is markedly reduced. This reduced binding capacity has no clinical implications under normal circumstances when sufficient vitamin K is present, since the FIX levels will still be within or only irrelevantly below the normal range. However, when patients with propeptide mutations are orally anticoagulated the lack of biologically active vitamin K combined with reduced binding of γ-carboxylase to the coagulation profactors results in a reversible clinically relevant bleeding diathesis days to weeks after initiation of VKA treatment. This bleeding diathesis is due to a rapid fall in FIX clotting activity (FIX:C), which falls to a disproportionately low level compared with the clotting activity of the other vitamin K-dependent coagulation factors. In fact, FIX:C levels fall so low that laboratory data mimic acquired haemophilia B [8]. As this bleeding disorder becomes manifest only in the presence of VKA, it has been referred to as "hypersensitivity to vitamin K antagonists" (VKA-HS). This term has recently been extended to other genetic variations such as point mutations of the CYP2C9, which result in bleeding diatheses due to overactivity of coumarins [10]. However, in the present study the term VKA-HS will refer to mutations in the factor IX propeptide only.

When patients with either of the mutations of FIX described above are treated with VKA, the bleeding diathesis is not detected by routine monitoring of the international normalised ratio (INR). The INR can be within or even below the targeted value at the time of bleeding. However, the sudden and disproportionately severe fall in FIX levels (<= 3%) induced by OAT leads to persistent abnormal prolongation of activated partial thromboplastin time (aPTT). VKA treated patients may present a prolonged aPTT. The severity of aPTT prolongation differs from patient to patient and depends on the laboratory methodology used. By "abnormal" we mean a prolongation that is unusual for the concurrent INR with a given methodology. The high morbidity and mortality associated with VKA treatment-related bleeding, and the possibility of detecting patients at risk by monitoring aPTT, has led to debate regarding the utility of screening all patients under VKA [11–13]. The main argument against screening is the presumed low prevalence of the mutation. We here report on the fourth and fifth Swiss patients with an Ala-10Thr mutation, who both presented with major bleeding under OAT. They belong to a family with one other proven heterozygote male (who has not been anticoagulated to date) and six women who are proven carriers of this X-linked recessive trait.

The purpose of this paper is to inform colleagues in Switzerland of the existence, frequency and pathobiology of this genetic mutation and to review issues such as treatment options for acute bleeding, anticoagulation of affected individuals and genetic testing in family members in the light of current data.

Subjects and methods

Subjects: The index patient was a 70-year-old (JU), highly active man in good general health who had to undergo aortic valve replacement due to severe aortic stenosis. A porcine aortic valve xenograft was successfully implanted. The immediate postoperative course was unremarkable and the patient was discharged 10 days later to a cardiac rehabilitation clinic with haemoglobin of 9 g/dL. His postoperative medications included OAT with phenprocoumon (planned for 3 months), aspirin, diuretics (spironolactone and loop diuretics), a beta-receptor blocker, an angiotensin-converting enzyme inhibitor and paracetamol. Shortly after starting cardiac rehabilitation his condition deteriorated. He developed progressive and very painful swellings of soft tissues, muscles and joints on legs and arms, together with bilateral pleural effusions. When this complications arose the patient's INR was 1.6;

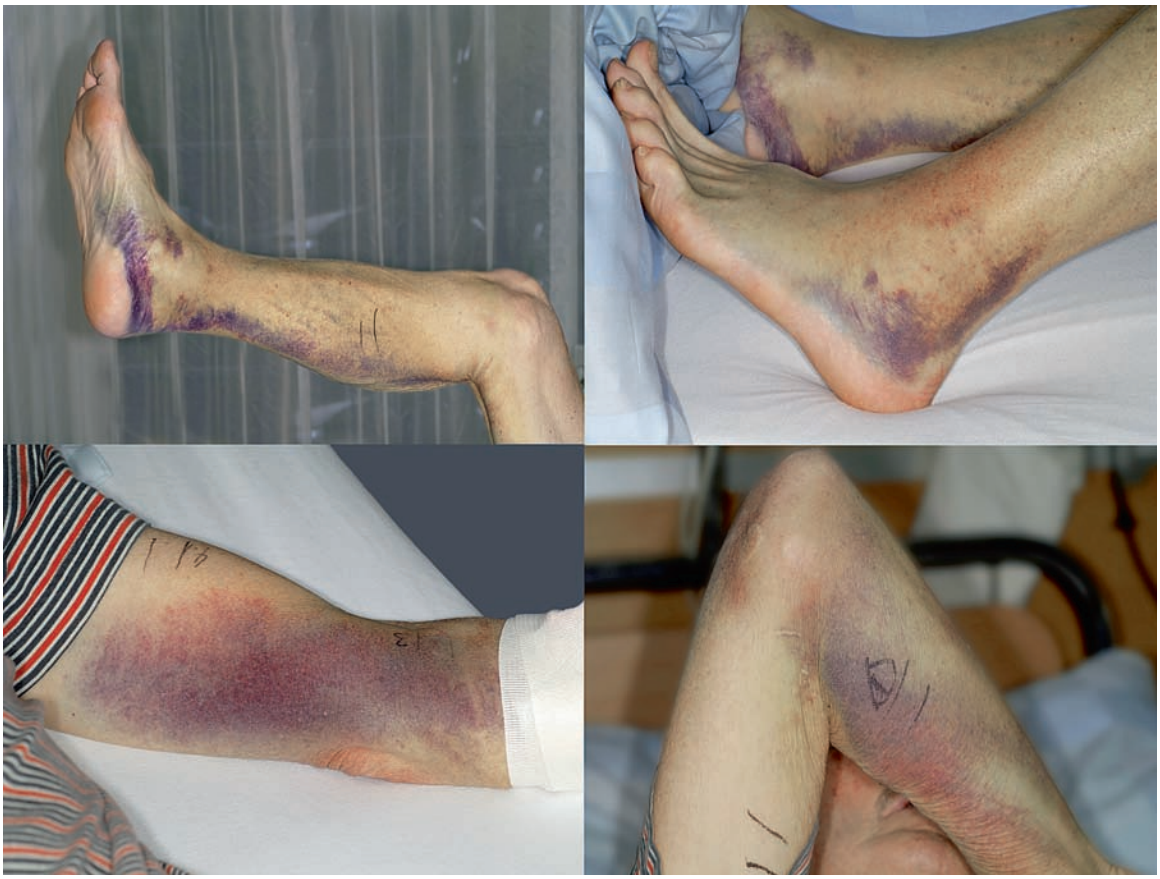

Figure 1

Extremities of the index patients with demarcated haematomas resembling haemophilia B photographed six days after diagnosis.

the platelet count was normal (182 G/L). He was readmitted to the University Hospital of Zurich for further investigation. The analgesic treatment with non-steroidal anti-inflammatory drugs was immediately stopped. All recorded INR values (range 1.5–2.5) had been in or just below the therapeutic range. His haemoglobin at the time of readmission was 8.1 g/dL. Despite daily blood transfusions this value dropped to 6.3 g/dL on day three of the hospitalisation. The neurological examination and pulse status of the extremities were normal. Echocardiography and Doppler sonography of the heart and great vessels revealed normal cardiac and graft function and no thrombosis of the great veins. A bleeding complication was suspected when the initially non-discoloured swellings turned into clinically evident haematomas and extensive testing was initiated in a search for a coagulation disorder (figure 1).

Family history: The family history revealed one brother and one sister previously exposed to OAT. The brother (WU), a farmer, had to be rehospitalised 5 weeks after a successful operative fixation of a left-sided traumatic patella fracture at the age of 56 years, due to severe muscle and joint bleeding of both lower extremities under OAT. His haemoglobin was 6.1 g/dL and he received packed erythrocyte transfusions. The patient slowly recovered after OAT was stopped.

Coagulation assays: Coagulation testing for patient JU was performed at the Coagulation Laboratory of Zurich University Hospital, an ISO 17025 accredited institution. Coagulation tests (activators, suppliers and remarks are given in parentheses) were run on a Dade Behring (DB), Coagulation System (DB, Marburg, Germany): aPTT (Actin FS, DB), INR (Innovin, DB), thrombin time (bovine thrombin, Diagnotec, Liestal, Switzerland; in-house assay), FVIII:C and FIX:C (Pathromtin SL; DB, aPTT-based assay), FII:C, FVII:C and FX:C (Innovin; DB, Quick-based assay), FXIII (Bercichrom FXIII, DB, functional assay), fibrinogen (Thrombin, DB, functional assay), Tinaquant D-dimer (Roche Diagnostics). The FIX inhibitor test was performed according to the Bethesda method [14].

Molecular genetic analysis of the FIX gene: Exon 2 of the FIX gene was analysed by amplification of a 161 bp fragment using the primers 5'-TTTCATGATGTTTTCTTTTTTGC-3' (nt 6270-6293) and 5'-TACATTCTCTCTAAGGTTCC-3' (nt 6410-6430). Amplified fragments were sequenced by means of the dideoxynucleotide chain termination method and the sequenase version 2.0 DNA sequencing kit (US Biochemical) [8, 15].

Results

Subjects: In the index patient, coagulation studies revealed an abnormally prolonged aPTT of 78 s (normal range 26–36 s), an INR of 2.1 under phenprocoumon therapy, elevated fibrinogen of 6.3 g/L (normal range 1.5–4 g/L)) and slightly elevated D-dimers of 1.7 µg/mL (normal range <0.5) (see table 1). Coagulation factor analysis revealed a markedly decreased FIX (2%), whereas FII and FVII were concordantly reduced to OAT (46 and 29% respectively). Other factors (factors V, VIII, XIII and von Willebrand) were within normal limits or not determined (FX).

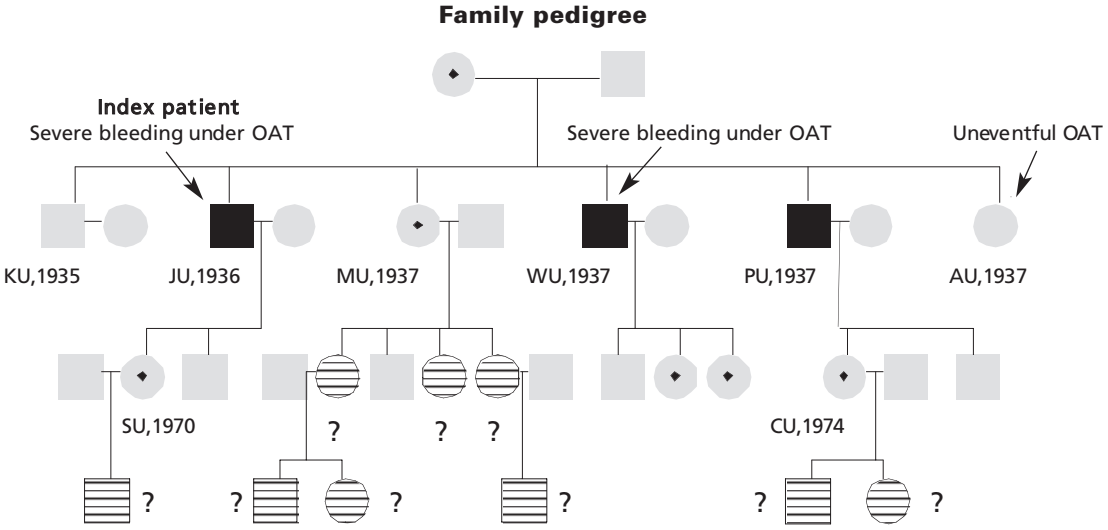

Figure 2

Circles are used for females, squares for males. Healthy individuals are depicted in bright grey, affected males in black and heterozygote carrier females in bright grey circles with an internal dot. Descendants possibly affected with an unknown genetic status are striped and have added question marks. Only family members with (possibly) affected descendants are followed to the next generation.

Acquired (antibody-induced) haemophilia B was excluded by negative test for FIX inhibiting antibodies (Bethesda test). In view of the laboratory test results a genetic alteration of the FIX propeptide was suspected. Oral anticoagulation with phenprocoumon was stopped. In view of the severity of the bleeding, the need to stop the active bleeding rapidly and the potential risk of thromboembolism associated with other treatment forms, we chose to administer two doses of factor IX concentrate (3000 IU of Immunine STIM plus [Baxter, Switzerland] followed 12 hours later by another dose of 1800 IU) intravenously. The patient subsequently recovered slowly but consistently from this painful bleeding disorder without recurrence.

Family history: A review of the hospital records from the index patient's brother (WU) revealed that the INR was consistently within the therapeutic range, whereas the aPTT was abnormally prolonged to 95s. No further coagulation factor measurements were performed at that time (1996). An extended family history revealed a sister (AU) who had undergone abdominal hysterectomy for cervical cancer at the age of 46 and received short-term OAT for three months postoperatively. No bleeding complication occurred. Three other siblings and their children had never received OAT to date, or suffered from bleeding disorders. Whole blood was obtained from three generations of family members, after obtaining written informed consent, and analysed for FIX mutations (figure 2).

Molecular genetic analysis of the FIX gene: We found the previously described genetic mutation of the FIX gene, Ala[GCC]-10Thr[ACC], in the index patient (JU) and his brother (WU), both with a bleeding history under OAT. One further heterozygote male and six female "carriers" were detected in the family. Apart from one female carrier who was exposed to OAT without a bleeding complication, no other individuals have been exposed to anticoagulation in the past. The pedigree and patient history are depicted in figure 2.

Discussion

The cases in context: We describe two patients with the threonine variant of a FIX propeptide mutation at locus -10 (Ala-10Thr; the wild type alanine is replaced by a threonine [figure 3]). Neither patient manifested a clinically relevant bleeding tendency in the absence of OAT. Both suffered "major bleeding" events shortly after OAT initiation and both had therapeutic or even subtherapeutic INR and an abnormally prolonged aPTT at the time of bleeding.

In one patient (JU) the FIX:C level was measured shortly after the bleeding complication became manifest and was found to be very low (2%). This disproportionately low FIX:C level is responsible for the abnormally prolonged aPTT and the acquired bleeding diathesis. He recovered well after cessation of OAT and transient substitution of FIX concentrate, and has remained in very good health with stable and normalised haemoglobin for more than 12 months now (report of primary care physicians).

FIX levels were not measured in the second patient at the time of bleeding, which occurred in 1996 – prior or just concomitant to the description of FIX propeptide mutations. In view of the positive family history, diagnosis of the propeptide mutation was made retrospectively by genetic analysis.

What therapeutic options are available in the event of acute bleeding?

We chose to treat our patient (JU) with FIX concentrate, since this treatment option instantly corrects the bleeding tendency without reducing

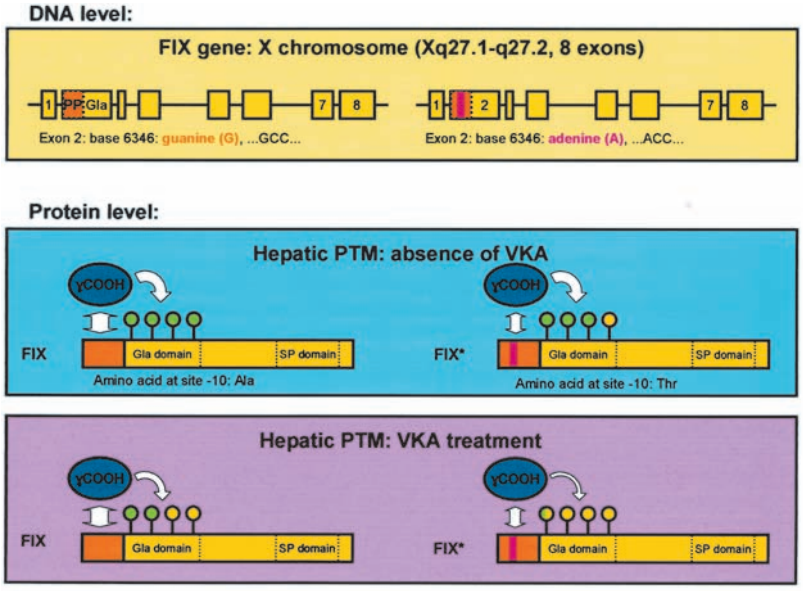

Figure 3

Model of vitamin K antagonist hypersensitivity (VKA-HS) in patients with Ala (-10)→Thr FIX propeptide mutation. This figure illustrates features of Ala (10)→Thr FIX-PM at the DNA level (yellow background) and at the protein level in the absence (blue background) or presence of VKA (purple background). Wild type FIX is depicted in the left column with Ala (10)→Thr FIX-PM in the right column. The strength of γ-carboxylase (γ-COOH) binding to the propeptide is indicated by the size of the double headed arrows, whereas carboxylase activity is symbolised by the size of the single headed arrows.
DNA level: The left represents the wild type FIX gene. The right depicts the relevant point mutation at basepair 6346 (depicted by a pink bar) in the propeptide domain (depicted in orange).
Protein level: Wild type FIX(alanine at locus -10, left column) permits optimal γ-COOH binding (large double headed arrow) and activity (large single headed arrow), resulting in complete γ-carboxylation status (illustrated by 4 green circles) and normal coagulation activity of the secreted FIX in the absence of VKA (blue background). In the presence of VKA treatment (purple background), γ-carboxylase activity (smaller single headed arrow) and consecutively FIX activity are reduced, resulting in the desired anticoagulation.
VKA-HS (tyrosine at locus -10 in the FIX-PM [right column]) results in normal or nearly normal γ-carboxylation status and coagulation factor activity in the absence of VKA treatment (blue background). However, in the presence of VKA treatment (purple background) the diminished γ-COOH/FIX* propeptide interaction related to the point mutation (see small white double headed arrow) and the absence of biologically active vitamin K result in severely reduced γ-carboxylation (yellow or partially yellow circles) and concordantly reduced FIX clotting activity.

the level of anticoagulation and is associated with minimal prothrombotic risk (only FIX:C is corrected while the anticoagulant effects related to low FII, FVII and FX are unaltered). In our view this was desirable as the patient had recently received a prosthetic heart valve. The major disadvantage of this treatment approach is its high cost. Since the patient's valve was of biological origin, long-term anticoagulation was not necessary and the patient could be discharged from hospital under anti-aggregation treatment by aspirin without anticoagulation.

Other therapeutic options for acute bleeding include vitamin K given intravenously or orally, fresh frozen plasma (FFP) and prothrombin complex concentrates (PCC). The low cost of vitamin K in this case was outweighed by the prothrombotic risk due to reversal of anticoagulation, poor predictability of response and slow treatment response (several hours). FFP and PCC also have an immediate effect, but cost and prothrombotic risk need to be considered. FFP cannot be used in patients at risk of left heart decompensation related to fluid overload. PCC, on the other hand, have a low risk of fluid overload but are more expensive and potentially more prothrombotic than FFP.

How can a mutation in a propeptide affect FIX clotting activity?

Propeptides are cleaved prior to the secretion of "mature" coagulation factors by the hepatocyte. The question thus arises of how a domain that is no longer present in the circulating coagulation factor can affect its biological activity. Figures 3 and 4 help to understand the pathophysiology of VKA-HS. The liver is the main source of plasma FIX. The FIX gene is located on the X chromosome and harbours eight exons depicted by yellow rectangles in figure 3 (DNA level) [3]. The gene translates into distinct domains including a signal peptide (encoded by exon 1), a propeptide (exon 2), a gla domain (exon 2), and the serine protease domain (exons 7 + 8). The FIX signal peptide targets the preproprotein to the endoplasmatic reticulum, where post-translational modification occurs at the glutamyl residues (glu, represented in figure 3 and figure 4 by yellow circles). The glu residues are thereby transformed into gla residues (represented by green or partially green circles in figure 3 and figure 4) with the aid of hepatic γ-carboxylase, a vitamin K-dependent enzyme. The carboxylation status of FIX – like that of all vitamin K-dependent coagulation factors – correlates with biological activity. In the presence of biologically active vitamin K γ-carboxylation is "processive". This involves an all-or-nothing phenomenon: a molecule either becomes carboxylated at all possible sites (human FIX has 12 such glutamyl sites) or remains non-carboxylated. High carboxylation renders the molecule biologically active, whereas low carboxylation status results in inactive vitamin K-dependent coagulation factors [16].

The anticoagulant effect of VKA is due to diminished activity of γ-carboxylase in the absence of vitamin K. VKA treatment also disrupts "processivity", resulting in non- or only partially γ-carboxylated FIX [5]. The low or absent

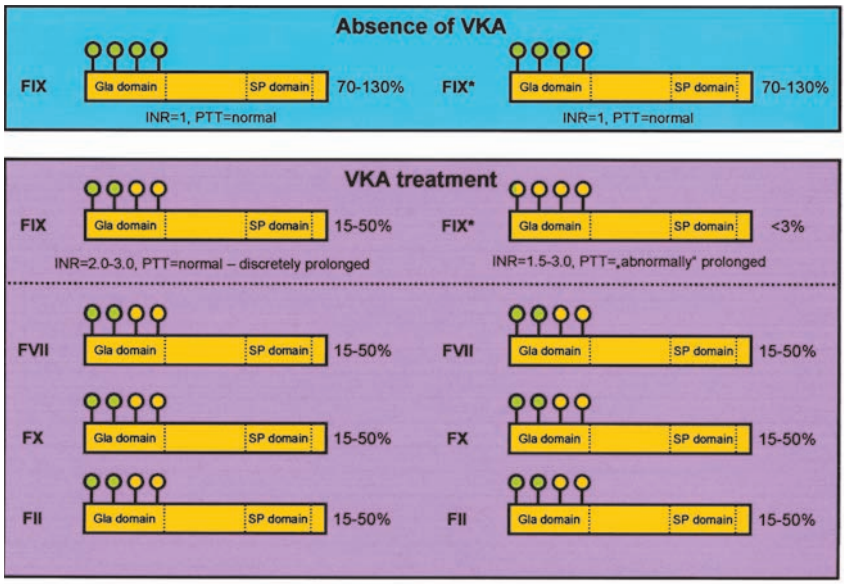

Figure 4

Plasma levels of vitamin K-dependent coagulation factors: Wild type FIX (left column) and FIX of patients with a FIX-PM (FIX*; right column) are depicted in the absence (blue background) and presence of VKA treatment (purple background). The amino acid sequence of circulating wild type FIX and FIX* is identical, the difference lying in the carboxylation status of the protein. In the absence of VKA treatment the FIX clotting activities in both conditions are normal or subnormal. Only in the presence of VKA treatment do FIX-PM patients acquire disproportionately low factor levels. The disproportionately low FIX levels translate into the abnormally prolonged aPTT observed in these patients. The percentages after the respective molecules indicate plasmatic clotting activity.

γ-carboxylation status leads to an altered three-dimensional structure of the coagulation factor, to impaired binding to activated surfaces and thereby to anticoagulation.

How frequent are FIX propeptide mutations?

Studies from Great Britain, the Netherlands, and Germany screened 1679 blood donors without finding an affected individual. This suggests a frequency of VKA-HS of below 1 in 1000. With our two cases, five patients with symptomatic VKA-HS have been described in Switzerland [6, 17, 18], two with the Ala→Val and three (including our patients) with the Ala→Thr mutation variant at locus 10 in the FIX propeptide. Although intensive inquiry about the patient's family history did not reveal a relationship between the present family and previously described cases [6, 18], we cannot rule out some distant kinship in earlier generations. From the reported cases the prevalence of VKA-HS due to mutations in the factor FIX propeptide in Switzerland can be estimated at approximately 1:1'000'000. The real prevalence is most probably even higher, due to underdiagnosis. Assuming that approximately 1% of the entire population is anticoagulated at any point in time (based on the incidences of the three main causes of OAT: atrial fibrillation, venous thromboembolism and valvular heart disease), and given that the mutation is only diagnosed in patients under OAT, we extrapolate a prevalence of the FIX propeptide mutation of above 1:100'000, possibly of 1:10'000.

A founder effect has been shown to exist in five previously described patients from Germany and Switzerland with the threonine variant of FIX PM. The original "founder" may have come from Switzerland. This would explain why a mutation that is rare elsewhere is "not so rare" in Switzerland [15].

How can the mutation be diagnosed?

Given the suspected frequency of the mutation, screening of the general population might not be a successful strategy [11–13]. A simple strategy might be to perform an aPTT in all patients with bleeding complications under VKA treatment. If the aPTT is found to be abnormally prolonged (whilst the INR might be in the target range or even below), a VKA-HS might be suspected. All laboratories can perform a 1:1 mixing study with normal pooled plasma which, in the event of normalisation of the INR (or aPTT), rules out an inhibitor. In our view, further investigation is warranted in the case of bleeding in VKA-treated patients in the presence of a therapeutic or near therapeutic INR and an abnormally prolonged aPTT, and where an inhibitor is ruled out by mixing studies.

Specialised laboratories can measure activities of individual clotting factors and perform inhibitor assays which will provide results suggestive of a propeptide mutation: FIX far below the expected range for an anticoagulated patient (all patients for whom we found results in the literature had FIX:C values below or equal to 3% with other vitamin K-dependent factors in the range of 15–60% in the presence of a normal FV:C); a Bethesda assay for an acquired FIX inhibitor was negative.

Finally, VKA-HS can be confirmed and family testing can be discussed. Given the high risk of bleeding associated with this mutation the relevance of identifying affected individuals is high. However, the basic principles of genetic testing (such as patient autonomy, informed consent, no testing of minors, amongst others) must be respected (www.samw.ch) [19].

It must be borne in mind that analysis of coagulation factor levels is not helpful in patients with a history of bleeding under VKA treatment

Table 1

Laboratory results of the index patient (JU).

	13.03.2006 Preop visit	30.03.2006 Discharge	22.04.2006 Readmission	25.04.2006	27.04.2007	28.04.2006	03.05.2006	normal range
Haemoglobin g/dl	14.8	9.0	6.3	7.5	9.3	10	11.5	13.4–17.0
Thrombocytes (G/l)	235	211	283	286	362	374	408	143–400
Quick (%)	106	29	30	31	25	59	79	70–120
INR (ratio)	1	2.2	2.1	2.1	1.6	1.4	1.2	n.a.
aPTT (s)	29		76	78	53	38	34	26–36
Fibrinogen (g/l)	3.4		5.7	6.2				1.5–4.0
D-dimer (µg/ml)			0.6	1.7				<0.50
FII:C (%)				46			106	60–150
FVII:C (%)				29			60	60–150
FIX:C (%)				2	18	26	29	50–200
FX:C (%)							68	60–150

Abbreviations and remarks: not applicable (n.a.), factor II clotting activity (FII:C), factor XIII functional activity (FXIII), von Willebrand factor ristocetin cofactor activity (vWF)

in whom the treatment was stopped or reversed some time previously, since FIX levels return to normal within days to weeks after VKA withdrawal or vitamin K administration. In the absence of VKA the diagnosis thus relies uniquely on detection of the mutation by the molecular biological approach.

Can affected individuals be anticoagulated?

Anticoagulation of patients with FIX propeptide mutations is associated with a high risk of complications. Hence, depending on the indication to anticoagulate, alternatives to OAK should be sought. In non-valvular atrial fibrillation aspirin has been shown to induce a 25% reduction in the risk of stroke and major vascular events in patients without prior stroke or TIA, with a number needed to treat of 1/100 [20]. In patients anticoagulated for venous thromboembolism low molecular weight heparins are a potential alternative to VKA. In patients with an imperative indication for anticoagulation, such as those with mechanical heart valves, one can consider replacing the mechanical valve with a bioprosthesis. A case report from Denmark described a patient with a mechanical valve who was anticoagulated with warfarin despite having a propeptide mutation [21]. The patient was managed by titrating anticoagulant treatment to FIX levels of 8–16%. These levels were based on the observation that haemophilia B patients rarely have thromboembolic events, and on the hypothesis that FIX levels slightly above the haemophilic range are protective of thromboembolism without the bleeding risk of haemophilia. Currently phase II and phase III trials are under way on direct oral anti-IIa and anti-Xa. Such VKA alternatives might become available in the near future, given that these drugs have proven their efficacy and safety in the long-term anticoagulation setting.

What about female carriers?

At present very little is known about the risk of oral anticoagulation in female carriers. In the literature we found one female carrier who was anticoagulated with VKA due to atrial fibrillation. While she had no bleeding complication, her FIX decreased to a minimum of 16% [17]. In our manuscript we report on the patients' heterozygote sister who underwent three months of oral anticoagulation without bleeding complications. This may suggest that the heterozygous mutation is biochemically only subtly overt and clinically silent due to one compensating normal allele. However, as the allele dominance might not be similar in all heterozygote females the risk of OAK should be weighed against the expected benefit. If VKA therapy must be prescribed we recommend close monitoring of anticoagulation including aPTT and FIX levels.

In conclusion, we present in this study a Swiss family with a recently described missense mutation of the FIX propeptide (Ala-10Thr) which is associated with severe bleeding complications under OAT. Major bleeding in any patient under OAT should be investigated; the presence of an abnormally prolonged aPTT should prompt further investigations. An abnormally increased aPTT in the presence of therapeutic or near therapeutic INR levels is the key element in establishing the relevant diagnosis. Treatment is aimed at reversing the haemorrhagic diathesis and depends on the indication for OAT. A disproportionate fall in FIX:C as compared to other vitamin K-dependent coagulation factors causes this congenital bleeding diathesis, also referred to as hypersensitivity to VKA. Inheritance of the disorder is X-chromosomal recessive. This syndrome can be classified as a special form of haemophilia B which manifests itself only under OAT. With nine proven cases and four untested but potentially affected juvenile males, our findings indicate

a relatively higher prevalence in Switzerland of a disorder whose potentially grave consequences and reversible nature warrant increased awareness on the part of primary care physicians.

Correspondence:
Dr. med. Silvia Ulrich
Department of Internal Medicine
Rämistrasse 100
CH-8091 Zürich
Switzerland
E-Mail: silvia.ulrich@usz.ch

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