Original Article

Factor V Leiden and venous thrombosis: First case report from Iraq

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Summary:

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Background: *Factor V Leiden mutation is the most common cause of hereditary thrombophilia . this mutation was found to be highly prevalent in the Eastern Mediterranean region , with recently reported prevalence of 3% in random Iraqi blood donors.*
Aim of study: *to document the case reports of factor V leiden in association with venous thrombosis in Iraqi patients .*
Sub. & Methods: *Six patients with Doppler confirmed Deep Venous thrombosis attending the Medical City Hospital were evaluated haemostatically and by PCR for the presence of factor Vleiden mutation. The patients had ages ranging between 22-60 years , and included 5 females and one male.*
Results: *Four were found to be heterozygous, while two were homozygous for this mutation by the DNA studies . the report includes a review of the relevant literature,and outlines the consensus opinion on indications of factor V leiden testing , and on the management of factor V Leiden associated Venous thombosis.*
Conclution: *All the cases in this report should have been routinely tested intinially for the factor V leiden mutation , & five out of them would be eligible candidates for long term or indefinite anticoagulation , with possible reduction in morbidity & recurrence risks .*

Introduction

Thrombophilia is defined as the tendency to develop thrombosis, as a consequence of predisposing factors that may be genetically determined, acquired or both (1) . prior to 1993, a hereditary cause for thrombophilia was only identified in 5-15% of patients, and was confined to deficiencies in Antithrombin,protein C and protein S(2). However,in 1993 , Dahiback and coworkers , described a novel mechanism for hereditary thrombophilia , which is characterized by poor anticoagulant response of the patient's plasma to Activated protein C (APC)(3), in what labeled "APC resistance phenomenon " . APC resistance was later found to be the most common risk factor associated with venous thrombosis found in 21-64% of patients (4,5). In 1994,ADutch team led by Rogier Bertina (6), confirmed that APC resistance

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Phenotype is due to a single point mutation in factor V gene at nucleotide 1691 with a G to A substitution this mutation results in a single amino acid change (Arginine to Glutamine) at position 506of the factor V molecule, changing it into "Factor V Leiden" . the latter position is a key cleavage site for APC , necessary for proper inactivation of activated factor V . Loss of this cleavage site will lead to accumulation of factor Va and increased thrombin generation and thus thrombophilic state. Factor V Leiden has variable distribution worldwide , being highly prevalent in Caucasian populations, but not in non-caucasians (e.g.Africans and East Asians) . High frequencies were especially reported from several Middle eastern countries , like Jorden , Syria , Lebanon ans Turkey, Suggesting the eastern Mediterranean basin may be the place where this mutation arose some 20000 to 34000 years ago (7-9). A prevalence of 3% for factor V leiden in Iraqi Blood donors has just been reported (10) , and the current paper documents the case reports of factor V leiden in association with venous thrombosis in Iraqi patients.

Material and Methods:

The six patients reported here , were Doppler confirmed cases of Deep Venous thrombosis , attending the Medical city – Baghdad for follow – up

or evaluation , in the period between 21st Sep.2002 and 12th feb.2003 .

All patients reported had a full relevant history taken , in addition to determination of their prothrombin times (Biomerieux), INR, Activated partial thromboplastin times (Cephalite-Biomerieux), and a second generation APC resistance test (Based on a method modified from STACLOT PC-R kit of Diagnostica Stago) . the Cut-off for APC resistance by the latter test was set at 48 seconds as detailed elsewhere (10) . the patients had their DNA extracted , Invitro amplified using Hybaid thermocycler (MWG) , then the amplified products were hybridized to allele-specific wild and mutant DNA oligonucleotide probes , and deteced by enzyme immunoassay according to the instructions of manufacturers (ViennaLab-Austria).

Case Reports:

Case no 1 (AH):

A 27 year old male , who was referred to the hematology department for haemostatic evaluation on the 21st nov. 2002 . the patient gave a long history of recurrent deep venous thrombotic episodes , with the first one occurring on the 29th Dec.1994 in his right leg, for which he was treated by heparin and warfarin , but developed left sided DVT one month later , while he treated by on therapy . his clinical condition improved , but one year later , he developed another attack of DVT , with leg ulceration after stopping the anticoagulant therapy . Over the next several years he had multiple attacks of DVT and one year ago he developed an attack of pulmonary embolism . throughout the past eight years , he received heparin followed by Warfarin after each thrombotic episode for variable periods . At the time of sampling he was not on any oral anticoagulants. The patient is the first of three brothers , both his brothers died , one at the sge of 27 years from a "heart attack" , while the other succumbed after strenuous exercise at the age of 23 years . the patient is neither diabetic nor hypertensive . He was found to be APC resistant by second generation tests (clotting time of 46 sec) , while his DNA studies revealed that he was homozygous for factor V Leiden mutation .

Case no 2 (FS):

A sixty year old female , who came on the 17th of Dec. 2002 for hemostatic evaluation stroke four months ago which on oral anticoagulant therapy . the patient had a history of ischemic stroke four months agowhich was followed within a month by Deep venous thrombosis , while she was on Warfarin . the patient gave a family history of venousthrombosis in a lower limb in a sister post – delivery , but no such previous history . the patient was on 3 mg/day Warfarin Sodium , at the time of sampling and was found to be resistant by Second Generation APC resistance test (Clotting time of 42 seconds), and her DNA testing revealed that she is Homozyous for factor V Leiden mutation .

Case no. 3(HH):

A 37 year married female who came for initial follow-up on the 25th of January 2003, while she was on anticoagulant therapy . the patient gave a history of right sided deep venous thrombosis of the lower limb (confirmed by Doppler) 7 days ago . the thrombosis occurred three days following delivery by caesarian section . the patient had no previous or family history of thrombosis and none of Diabetes mellitus or hypertension . she is currently on heparin and just started Warfain 5 mg/day . the patient was found to be APC resistant by second generation APC tests (clotting time of 48 sec) , her DNA studies revealed heterozygosity for factor V Leiden .

Case no 4 (AM) :

A 52 year old female who came on the 22nd January 2003 for haemoststic evaluation of anticoagulation therapy . the patient gave a history of recurrent episodes (more than 10 attacks) of deep venous thromboses of the lower limbs occurring over the past 20 year .Some of these attacks occurred spontaneously , while others followed pregnancies . Her latest attack occurred 3 months ago . Some of her later attacks of venous thrombosis were Doppler confirmed . the patient had no family history of venous thrombosis . She was neither diabetic nor hypertensive . She was on 3 mg Warfarin at the time of sampling , and she was resistant by second generation tests (clotting time of 43 sec.) .her DNA Studies revealed that she is heterozygous for factor V Leiden mutation .

Case No. 5(SK):

A 22 year old married female , who came on the 21st Sep. 2002, for hemostatic evaluation while she was on oral anticoagulant therapy . the patient gave a history of Doppler confirmed Deep Venousthrombosis of the right leg, one month ago , for which she received a seven day course of Intravenous heparin , followed by Warfarin sodium the patient was on 5 mg/day Warfarin at the time of sampling. The patient has been married for the two years , and had her first pregnancy complicated by pre-eclampsia, intrauterine death and therapeutic was instituted 10 months ago . She had a family history of deep venous thrombosis , in a brother and a sister , both before the age of 40 years , but no such previous personal history . the patient was found to be APC resistant by second generation tests(Clotting time of 44 sec). DNA studies revealed that she was heterozygous for factor V Leiden mutation .

Case No 6 (NH) :

A 28 year old unmarried female , who was referred on the 12th of Feb. 2003 , for haemostatic evaluation , just before instituting anticoagulant therapy . the patient has sustained a Doppler confirmed

spontaneous Deep Venous thrombosis of her Left leg 2 days earlier . She had no previous personal or family history of Venous thrombosis . She was not hypertensive or Diabetic and was on no therapy at the time of Sampling . She was found to be resistant by second generation APC-R tests (47 sec), and her DNA studies revealed heterozygosity for Factor V Leiden mutation . Table (1) outlines some of the main parameters in the six Iraqi Factor V Leiden carriers reported.

Discussion:

Factor V Leiden (FVL) is the most common cause of hereditary thrombophilia in causcsian populations . the major clinical manifestation is Deep Venous thrombosis with or with out pulmonary embolism . there is also an increased risk of cerebral vein thrombosis and although controversial , of recurrent fetal loss and certain obststric complications (11) . Heterozygotes for the V Leiden mutation have been found to have an overall seven folds increased risk of venous thromboembolism (VTE) , while homozygotes have an 80 folds increased risk , compared to non – carriers (12) .

Two of the six reported cases above were homozygous, while four were heterozygous for the factor V Leiden mutation , the age of onset of the first thrombotic event varied between 19 and 60 year. All four heterozygous patients had their first attack at their third or fourth decades , and interestingly all were females . this is consistent with the age patterns reported in Western studies , where the peak risk for thrombosis in factor V Leiden heterozygous females occurred between the ages of 20 and 40 years , while it occurred in 41-60 age group in heterozygous males (13) . this difference between males and females , is due to the additional acquired thrombotic risk related to pregenancy ,puerperium and oral contraceptive in the child – bearing age (13) . In accordance with the latter statemen , two of the four Iraqi heterozygous carriers reported , had their thrombotic episodes post – parteum , one of whom post – Caesarian . On the other hand , the episodes of thrombosis tend to occur in homozygous FVL carriers at younger median ages , than heterozygotous ones (12) , thus their occurrence at the age of 19 in patient 1 (AH) is expected . While their occurrence in a sixty year old patient (No.2,FS) , has its matches in literature , and actually it that some homozygous may still be asymptomatic beyond the age of 60 years , and few may even get throughout their lifetime without sustaiing any thrombotic event , despite exposed to many risk situations (13,14) . this appears to be related to the fact the FVL is a mild risk factor per se , and that the probability of developing thrombosis is relatively dependent on the occurrence of an acquired or inherited risk situation (15) . patient 2 (FS) , had her first thrombotic venous episode in the context of an acquired risk situation , which is immobilization related to ischaemic strocke , in addition to age – related risk . It is important here to note that FVL has been reported in association with ischaemic strocke , although most large series failed to confirm a significant (16) . Furthemore , the detection of FVL mutation in a 60 year old with a first VTE episode , is consistent with the view that older persons should not be excluded from FVL screening (17) .

Family history in a first degree relative was reported in both homozygous and one of the four heterozygous cases .the absence of such history in three remaining heterozygous cases , is mostly due to the mild thrombotic risk related to this mutation , and actually majority of heterozygotes (about 90%) may not develop any thrombotic event throughout their lifetime (14,15) .

History of recurrent DVT was documented in one of the heterozygous and one of the homozygous cases , and while the risk of recurrence in FVL homozygous patients is significantly increased (18) , the increased risk in heterozygous patients has been demonstrated in some studies , but was disputed by others(19,20) .

The Importance of detevtion of factor V Leiden mutation , is that it would in some situations , directly alter clinical management of the proband , or lead testing of other family members , and testing for it , is highly recommended in those with history of recurrent VTE , those with first VTE before the age of 50 years , those with a first unprovoked VTE (at any age) , or VTE at unusual sites , VTE related to pregnancy , puerperium or oral contraceptive use , or those with a family history of VTE in a first degree (11) . and although the initial management of an acute first attack VTE in a FVL carrier should not be different from non – carriers , certain categories of FVL carriers should receive indefinite anticoagulation , while others should receive appropriate propgylaxis duringspecific thrombotic risk situations (e.g. pregnancy , major surgery and immobilization) . Candidates for indefinite anticoagulant therapy include those carriers with an idiopathic or life threatening VTE events , homozygous carriers or double heterozygous ones (for more than one inherited thrombophilic defect) , and those carriers with a persistent clinical risk factors (e.g. malignancy or anti-phospholipid antibodies)(11) . Such recommendation should be tailored to particular patients .

All the cases in this report , based on the recommendations above , should have been routinely tested initially for the factor V Leiden mutation , and five out of them would be eligible candidates for long-term or indefinite anticoagulation , with possible reduction in morbidity and recurrence risks .

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Case no. (initials)	Age at first thrombotic episode	Sex	ABO Group	INR	APTT (sec)	2nd Generation APC-R clotting time (sec)	Genotyping for V Leiden mutation
1(AH)	19	M	B	1.0	31	46	Homozygous
2(FS)	60	F	A	1.9	33	42	Homozygous
3(HH)	37	F	B	1.4	28	48	Homozygous
4(AM)	32	F	A	1.5	30	43	Homozygous
5(SK)	22	F	O	2.5	46	44	Homozygous
6(NH)	28	F	O	1.0	30	47	Homozygous

Table (1) An outline of the main clinical and laboratory finding in the six factor V Leiden carriers