

Severe thrombophilic diathesis starting with hepatic vein thrombosis (BUDD-CHIARI syndrome) in a family with a new Protein S gene mutation

P. Gruselle¹, P. Ooghe¹, P. Cauchie², G. Van der Cruyssen³

(1) Department of Hepato-Gastro-Enterology, Vesale Hospital, CHU de Charleroi ; (2) Department of Clinical Biology, Vesale Hospital, CHU de Charleroi ; (3) Center for Medical Genetics, Ghent University Hospital, Belgium.

Abstract

We report the case of a 26-year-old man with a chronic Budd-Chiari syndrome (BCS) with ascites, caused by a hereditary Protein S (PS) deficiency, in a Turkish family with consanguinity.

In this family, the father, the two sisters and the young brother suffered from severe venous thrombosis of the limbs, with pulmonary embolism in two of them.

Those thrombotic events are caused by a hitherto not reported mutation in the PROS 1 gene on chromosome 3, resulting in a severe familial PS deficiency.

No other thrombophilic defect was detected in the family, despite extensive investigation.

Furthermore, we observe hereditary twenty-nail dystrophy in this family, the two genes probably segregating independently.

Prophylaxis is discussed. (*Acta gastroenterol. belg.*, 2006, 69, 20-24).

Introduction

Budd-Chiari syndrome (BCS) is defined by the European Group for the Study of Vascular Disorders of the Liver as "hepatic venous outflow obstruction at any level from the small hepatic veins to the junction of the inferior vena cava and the right atrium, regardless of the cause of obstruction" (1).

This rare disorder, with a lot of underlying and very often multiple and heterogeneous etiologic factors (2-7), is frequently associated with a severe prognosis (8-12).

Because of this frequent association of multiple concurrent factors, particularly various thrombogenic conditions, a comprehensive investigation is recommended for primary BCS (1,2-7,11,12).

Hereditary Protein S (PS) deficiency, caused by a gene defect, more particularly in the PROS 1 gene on chromosome 3, is a high risk factor for venous thrombosis generally speaking (13-17), but accounts for less than 5% of BCS patients (1,2-7,11,12).

We describe a BCS patient in a family affected by severe thrombotic events, even at young age, and a very low free Protein S level, with an extensive familial inquiry, search for other prothrombotic states and triggering events, and study of the PROS 1 gene.

Anti-thrombotic treatment in the affected relatives is discussed.

Case report

A 26 year-old Turkish man (OO), carpenter, drinking no alcohol, taking no medication, is admitted for a tense ascites with severe asthenia.

This ascites, with very few cells at examination and a high (3.6 g/dl) protein level (4), with oesophageal varices grade II at gastroscopy, contrasts strongly with a relatively well preserved hepatic function :

Prothrombin time 73%, Albumin 4.16 g/dl, Aminopyrin breath test 3.5% (normal range : 4-8%). AST and ALT are normal, Alkaline phosphatase : 357 (100-280), Gamma GT : 167, Bilirubin : 1.8 mg/dl, Gamma Globulins : normal.

Abdominal CT-scanner and MRI show a very severe diffuse hepatopathy with major parenchymatous changes : atrophy of right liver lobe ; hypertrophy of left liver lobe and caudate lobe, with very heterogeneous aspect, and blurred areas not enhanced after contrast injection ; irregular liver outlines ; massive ascites ; compression of inferior vena cava ; two wide and patent left hepatic veins ; no flow in the right and median hepatic veins ; wide dilation of the left para-vertebral venous system (Fig. 1 and 2).

Doppler ultrasonography shows the same appearance of the hepatic veins and inferior vena cava. Wide and tortuous collateral veins are observed in the sub-capsular area of the right liver lobe, as intra-hepatic venous anastomoses (11). Venous flow is antegrade but slow (< 10 cm/sec) in the portal vein and the left portal vein, but segmental retrograde in the right portal vein. A respiratory inversion of portal flow ("back and forth" flow) was sometimes observed (18).

Sus-hepatic catheterisation with phlebography confirm those data about the hepatic veins, and also shows :

- a major extrinsic compression of inferior vena cava.
- ectasias of hepatic veins and multiple intra-hepatic venous anastomosis.

Correspondence : Dr. Paul Gruselle, Chef de service associé, Service d'Hépatogastro-entérologie, CHU de Charleroi - Hôpital Vésale, rue de Gozée, 6110 Montigny le Tilleul, Belgium. E-mail : paul.gruselle@chu-charleroi.be.

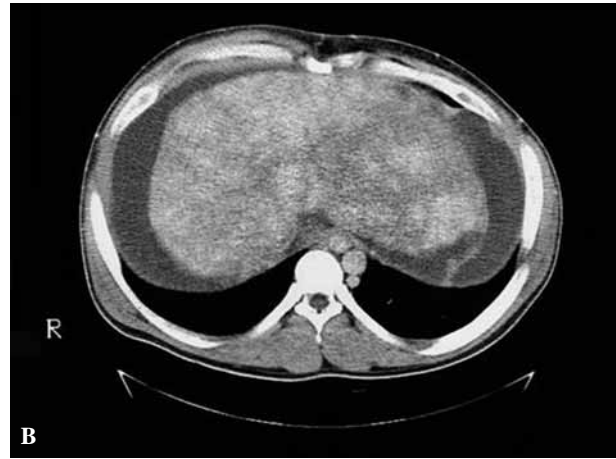
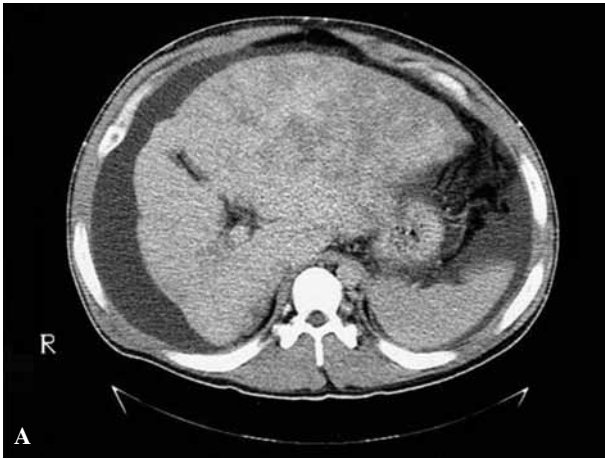


Fig. 1, A-B. — CT-scanner : atrophy of right hepatic lobe - hypertrophy of left hepatic lobe with very heterogeneous parenchyma and blurred areas not enhanced after contrast injection – ascites – irregular liver outlines : Budd-Chiari Syndrome.

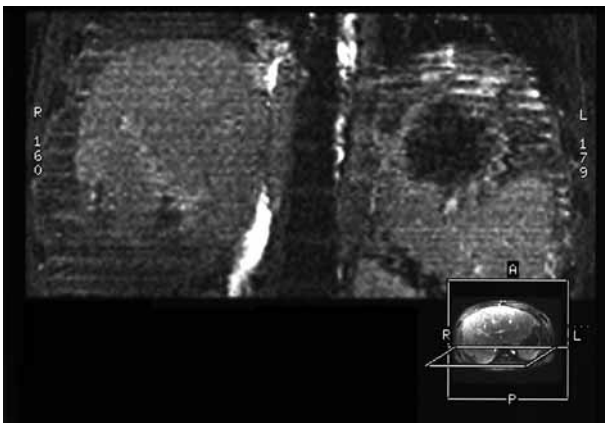


Fig. 2. — MRI : extreme compression of the inferior vena cava by the liver (very probably by Spiegel lobe). Strongly dilated left para-vertebral venous plexus (collateral drainage veins).

- a severe portal hypertension, with a wedged hepatic venous pressure at 35 mm HG (N : 4-11) (free hepatic venous pressure unfortunately not noted).

Liver biopsies by catheterisation of the patent left hepatic vein shows :

- dilation and congestion of centrolobular sinusoids with compression and rarefaction of hepatocytes rows(drop-out)
- bridging fibrosis with proliferation of biliary neo-canaliculars (Fig. 3)

No other cause of hepatopathy is found : viral, immune, metabolic, toxic, neither cardiac. The diagnosis of BCS (hepatic vein thrombosis) is obvious (5,10-12), also strengthened by the existence of intra-hepatic venous anastomoses and sub-capsular venous collateral veins (11,18).

Laboratory tests reveals a free PS deficiency of 27% (N : 70-130), in absence of severe liver failure (see laboratory data above).

At extensive investigation, no other thrombophilic factor is observed, especially concerning :

Protein C or antithrombin III ; homocystein and folic acid ; anti-phospholipid lupus antibody ; paroxysmal nocturnal hemoglobinuria ; factor V R 506 Q mutation (factor V Leiden) ; prothrombin gene 20210 A mutation.

Despite a mild polyglobulia (hemoglobine : 16.9 g/dl – hematocrite : 51.4), no myeloproliferative disease, patent or occult, was observed-

in particular, no spontaneous growth of erythroid precursors in culture in the absence of erythropoïetin (7,19).

Caryotype is normal.

The patient was treated and maintained in steady state (severe asthenia, ascites and pleural effusion) with paracentesis, furosemide, spironolactone, propranolol, subcutaneous low-weight heparine first, then warfarin, lactulose. He died three years later in a car crash, under warfarin treatment.

Family inquiry

Some months and years later, observing severe thrombotic events in this family, we did a family inquiry, summarised in Table 1.

The disease is transmitted by the father, whose free PS level is 20%, and who, 52 years-old, will experience a spontaneous severe superficial venous thrombosis of the upper limb.

The mother has a free PS at 92% and is asymptomatic.

The first sister, 20 years-old, while on oral contraceptives, suffered a deep venous thrombosis of lower leg with severe pulmonary embolism, with free PS : 21%.

The young sister had the same problem in post-partum, with free PS : 17%.

The youngest brother, 17 years-old, suffered deep and superficial venous thrombosis, with free PS : 17%.

Note that total PS is normal or only slightly lowered in affected relatives (Table 1) (24).

EN COULEUR ?

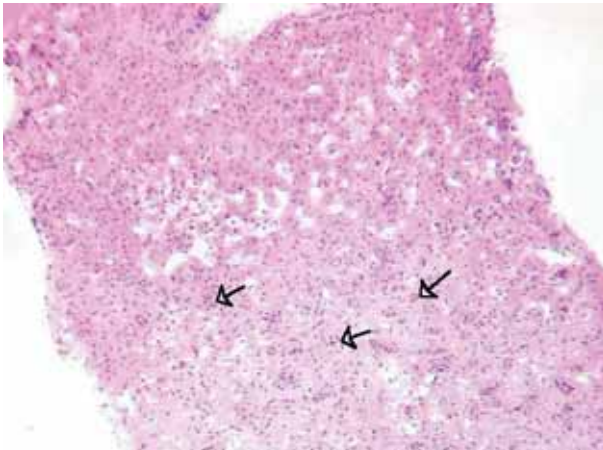


Fig. 3. — Dilation and congestion of centro-lobular sinusoids with “drop out” – bridging fibrosis with proliferation of biliary neo-canallicules.



EN COULEUR ?

Fig. 4. — Familial twenty-nail dystrophy

Table 1. —

Patient	Year of bearth	Diagnosis	Age of beginning	Free Prot. S 70-130	Coagulating Prot. S. 65-140	Total Prot. S. 70-130	Mutation c.1388 delT	Ungual dystrophy
Father : OV	1947	SVT of upper limb	52	20	33	67		NO
Mother : OT	1950	NIHIL		92	122	115		NO
Patient : OO	1970	BUDD-CHIARI	26	27	43	66		NO
Sister : OG	1976	DVT + PE (oral contraceptives)	20	21	25		YES	YES
Sister : OE	1979	DVT + PE (post-partum)	21	17	30	60	YES	NO
Brother : OH	1985	DVT + SVT	17	23	34	75	YES	YES

Those three young siblings were examined extensively, with no other coagulation abnormality and negative research for factor V R 506 Q mutation (factor V Leiden) and prothrombin gene 20210 A mutation.

- (NB : heterozygoty for MTHFR gene C 677 T mutation, probably without clinical significance, in the youngest sister).

The genetic study

(Ghent University Hospital) revealed the gene defect responsible for this hereditary PS deficiency : the PROS 1 gene of the three younger siblings was analysed (Table 1) for mutations by direct sequencing of PCR amplification products of the coding sequence (exons 3 to 15) and introns borders, essentially as described (15).

In the DNA of all three siblings, a single nucleotide deletion at the nucleotide position “1242” (c DNA level), was detected, namely c.1242 delT in exon 11, which

gives rise to a frame shift and a premature translation stop codon 84 nucleotides downstream of the deletion.

This mutation, resulting in a severe PS deficiency with thrombophilia, has not yet been reported to the best of our knowledge – see database of mutations with PS deficiency (17).

The unguinal dystrophy

A congenital twenty-nail dystrophy, verging on unguinal agenesis (Fig. 4), is known in some members of this family : namely in our patient and his two sons, in one of his sisters and in his brother – and is missing in the second sister, in the father and mother (Table 1).

The family is originating from Turkey ; the parents of the patient are first cousins (consanguinity).

The unguinal dysplasia is of micronychchia type, described since 1925 in an autosomic dominant form (20-23), and studied in the Mc Kusik catalogue (OMIM).

An extensive research did not find any described association between those two genetic abnormalities. The genealogy strongly suggests the independent segregation of the two conditions : the twenty-nail dystrophy (mode of inheritance not clear) and the PS deficiency (autosomal dominant inheritance). Autosomal dominant inheritance of the twenty-nail dystrophy is possible if non-penetrance is supposed for the index patient OO and for his parents. Autosomal recessive inheritance is probably the best hypothesis. In that case, it is possible the index patient and his wife were consanguineous (although we didn't obtain this information) and were carriers of the defect of the nail dystrophy.

Discussion

The commonly recognized causes for BCS are hereditary or acquired prothrombotic states, particularly :

- primary myeloproliferative disorders
- Protein C deficiency, factor V Leiden and antiphospholipid syndrome – and, less often, prothrombin gene mutation, paroxysmal nocturnal hemoglobinuria, methylene-tetrahydrofolate reductase (MHTFR) gene mutation or other conditions (1-3, 10-13).

A combination of a number of those prothrombotic factors is extremely frequent (12).

Oral contraceptive use, pregnancy, an inflammatory state may play an additional role ; a local factor is rarely (5%) identified (12).

Protein S (PS) deficiency accounts for less than 5% of BCS patients (1,2-7,11,12), although it is common in patients with portal vein thrombosis (3,12) and also a high risk factor for venous thrombosis generally speaking (13-17,24).

PS deficiency is mostly hereditary with phenotypic variability between families with gene defect, but decreased PS can also arise from acquired conditions such as liver failure, coumadin treatment, consumption from thrombosis, oestrogen therapy, pregnancy, orthotopic liver transplant, chickenpox infection (24-30).

We report a severe thrombophilic diathesis starting with BCS in a family with a hitherto not reported PS gene mutation.

Observed free PS levels are low and, as reported, type I and III were observed (total PS levels borderline) (Table 1) (24).

All affected members are severely symptomatic, even at young age (however, two accidents had triggering events : oral contraceptives or post-partum).

No other thrombophilic defect neither myeloproliferative syndrome was detected, despite extensive investigations.

Each of the children of carriers of the PROS 1 mutation have a 50% risk of having inherited the PS deficiency.

Early diagnosis with free PS plasma determination seems essential within the family members (15-24), with confirmation by genetic analysis of the familial PROS 1 mutation.

In patients with Budd-chiari syndrome complicating prot S deficiency, a systematic and "ad vitam" anticoagulation is necessary.

The use of primary prophylaxis is discussed in the literature, actually until today with a poor response. However, due to the very severe events associated with this mutation, new generation anticoagulant (direct thrombin inhibitors like ximelagatran) (31,32) must surely be considered when available.

Acknowledgement

We are grateful to Dr. L. Van Maldergem and Dr. C. Fourneau (IPG - Institut de Pathologie et de Génétique, Lovreval, Belgium) and to Dr. Y. Doffiny (dermatologist, Marchienne-au-Pont) for their help.

References

1. JANSSEN H.L., GARCIA-PAGEN J.C., ELIAS E., MENTHA G., HADENGUE A., VALLA D.C. Budd-Chiari syndrome : a review by an expert panel. *Journal of Hepatology*, 2003, **38** : 364-371.
2. JANSSEN H.L., MEINARDI J.R., VLEGGAR F.P., VAN UUM S.H., HAAGSMA E.B. VAN DER MEER F.J., VEN HATTUM J., CHAMULEAU R.A., ADANG R.P., VANDENBROUCKE J.P., VAN HOEK B., ROSENDAAL F.R. Factor V Leiden mutation, prothrombin gene mutation, and deficiencies in coagulation inhibitors associated with Budd-Chiari syndrome and portal vein thrombosis : results of a case-control study. *Blood*, 2000, **96** : 2364-8.
3. DENNINGER M.H., CHAIT Y., CASADEVALL N., HILLAIRE S., GUILLIN M.C., BEZEAUD A., ERLINGER S., BRIERE J., VALLA D. Cause of portal or hepatic venous thrombosis in adults : the role of multiple concurrent factors. *Hepatology*, 2000, **31** : 587-91.
4. DE B.K., DE K.K., SEN S., BISWAS P.K., DAS T.K., HAZRA B. Etiology based prevalence of Budd-Chiari syndrome in eastern India. *J. Assoc. Physicians India*, 2000, **48** : 800-3.
5. MENON N., SHAH V., KAMATH P. The Budd-Chiari syndrome. *N. Engl. J. Med.*, 2004, **350** : 578-585.
6. MOHANTY D., SHETTY S., GHOSH K., PAWAR A., ABRAHAM P. Hereditary thrombophilia as a cause of Budd-Chiari syndrome : a study from Western India. *Hepatology*, 2001, **34** : 666-670.
7. VALLA D., CASADEVALL N., LACOMBE C., VARET B., GOLD-WASSER E., FRANCO D., MAILLARD J.N., PARIENTE E.A., LEPORRIER M., RUEFF B., MULLER O., BENHAMOU J.P. (Clichy, Paris, Villejuif, Colombes, Orléans and Caen, France). Primary myeloproliferative disorder and hepatic vein thrombosis. A prospective study of erythroid colony formation in vitro in 20 patients with Budd-Chiari syndrome. *Ann. Intern. Med.*, 1985, **103** : 329-334.
8. MURAD S.D., VALLA D.-CH., DE GROEN P.C., ZEITOUN G., HOPMANS J.A.M., HAAGSMA E.B., VAN HOEK B., HANSEN B.E., ROSENDAAL F.R., JANSSEN H.L.A. Determinants of survival and the effect of portosystemic shunting in patients with Budd-Chiari syndrome. *Hepatology*, 2004, **39** : 500-508.
9. ZETOUN G., ESCOLANO S., HADENGUE A., AZAR N., EL YOUNSI M., MALLET A., BOUDET M.J., HAY J.M., ERLINGER S., BENHAMOU J.P., BELGHITI J., VALLA D. Outcome of Budd-Chiari syndrome : a multivariate analysis of factors related to survival including surgical portosystemic shunting. *Hepatology*, 1999, **30** : 84-89.
10. LANGLET P., ESCOLANO S., VALLA D., COSTE-ZEITOUN D., DENIE C., MALLET A., LEVY V.G., FRANCO D., VINEL J.P., BELGHITI J., LEBREC D., HAY J.M., ZEITOUN G. Clinicopathological forms and prognostic index in Budd-Chiari syndrome. *J. Hepatol.*, 2003, **39** : 496-501.
11. VALLA D. The diagnosis and management of the Budd-Chiari syndrome : consensus and controversies. *Hepatology*, 2003, **38** : 793-803.

12. VALLA D. Vascular disorders of the liver. *Acta Gastroenterol. Belg.*, 2003, **66** : 294-297.
13. FAIONI ELENA M., VALSECCHI C., PALLA A., TAIOLI E., RAZZARI C., MANNUCCI PIER MANNUCCIO. Free protein S deficiency is a risk factor for venous thrombosis. *Thromb. Haemost.*, 1997, **78** : 1343-1346.
14. BORGEL D., GANDRILLE S., AIACH M. Protein S deficiency. *Thromb. Haemost.*, 1997, **78** : 351-6.
15. MESSIAEN L., CALLENS T., BAELE G. Identification of two different mutations causing protein S deficiency in two unrelated Belgian families using a nonisotopic scanning and sequencing method. *Haemostasis*, 1997, **27** : 228-236.
16. SCHUETZE S.M., LINENBERGER M. Acquired protein S deficiency with multiple thrombotic complications after orthotopic liver transplant. *Transplantation*, 1999, **27** : 1366-9.
17. GANDRILLE S., BORGEL D., SALA N., ESPINOSA-PARRILLA Y., SIMMONDS R., REZENDE S., LIND B., MANNHALTER C., PABINGER I., REITSMA P.H., FORMSTONE C., COOPER D.N., SAITO H., SUZUKI K., BERNARDI F., AIACH M., Plasma coagulation inhibitors subcommittee of the scientific and standardization committee of the international society on thrombosis and haemostasis. Protein S deficiency : a database of mutations – summary of the first update. *Thromb. Haemost.*, 2000, **84** : 918.
18. CAZALS-HATEM D., VILGRAIN V., GENIN P., DENNINGER M.H., DURAND F., BELGHITI J., VALLA D., DEGOTT C. Arterial and portal circulation and parenchymal changes in Budd-Chiari syndrome : a study in 17 explanted livers. *Hepatology*, 2003, **37** : 510-9.
19. HIRSHBERG B., SHOUVAL D., FIBACH E., FRIEDMAN G., BEN-YEHUDA D. Flow cytometric analysis of autonomous growth of erythroid precursors in liquid culture detects occult polycythemia vera in the Budd-Chiari syndrome. *J. Hepatol.*, 2000, **32** : 574-578.
20. HAZELRIGG D.E., DUNCAN W.C., JARRATT M. Twenty-nail dystrophy of childhood. *Arch. Derm.*, 1977, **113** : 73-75.
21. PAVONE L., LI VOLTI S., GUARNERI B., LA ROSA M., SORGE G., INCORPORA G., MOLLICA F. Hereditary twenty-nail dystrophy in a sicilian family. *J. Med. Genet.*, 1982, **19** : 337-340.
22. THOMPSON H.B. Hereditary dystrophy of the nails. *JAMA*, 1928, **91** : 1547.
23. TOBIAS N. Hereditary familial dystrophy of the nails. *JAMA*, 1925, **84** : 1568-1569.
24. MAKKRIS M., LEACH M., BEAUCHAMP N.J., DALY M.E., COOPER P.C., HAMPTON K.K., BAYLISS P., PEAKE I.R., MILLER G.J., PRESTON E. Genetic analysis, phenotypic diagnosis, and risk of venous thrombosis in families with inherited deficiencies of protein S. *Blood*, 2000, **95** : 1935-1941.
25. ESPINOSE-PARILLA Y., YAMAZAKI T., SALA N., DAHLBACK B., DE FRUTOS P.G. Protein S secretion differences of missense mutants account for phenotypic heterogeneity. *Blood*, 2000, **95** : 173-179.
26. ANDERSEN B.D., BISGAARD M., LIND B., PHILIPS M., VILLOUTREIX B., THORSEN S. Characterisation and structural impact of five novel PROS1 mutations in eleven Protein S-deficient families. *Thromb. Haemost.*, 2001, **86** : 1392-9.
27. ALMAZY L., SORIA J., SOUTO C., COLL I., BACQ D., FAURE A., MATEO J., BORREL M., MUNOZ X., SALA N., STONE W.H., LATHROP M., FONTCUBERTA J., BLANGERO J. Genetic analysis of idiopathic thrombophilia project. A quantitative trait locus influencing Free plasma Protein S levels on human chromosome 1q : results from the Genetic Analysis of Idiopathic Thrombophilia (GAIT) project. *Arterioscler. Thromb. Vasc. Biol.*, 2003, **23** : 508-511. Epub, 2003 Jan 9.
28. REZNDÉ S., LANE D., ZÖLLER B., MILLE-BAKER B., LAFFAN M., DAHLBACK B., SIMMONDS R.E. Genetic and phenotypic variability between families with Hereditary protein S deficiency. *Thromb. Haemost.*, 2002, **87** : 258-65.
29. SCHUETZE S.M., LINENBERGER M. Acquired protein S deficiency with multiple thrombotic complications after orthotopic liver transplant. *Transplantation*, 1999, **67** : 1366-69.
30. CAMPANELLI A., KAYA G., OZSAHIN AH., LA SCALA G., JACQUIER C., STAUFFER M., BOEHLEN F., DE MOERLOOSE P., SAURAT J.H. Purpura fulminans in a child as a complication of chickenpox infection. *Dermatology*, 2004, **208** : 262-4.
31. BERGSRUD E., GANDHI P. A review of the clinical uses of Ximelagatran in thrombosis syndromes. *J Thromb Thrombolysis.*, 2003, **16** : 175-88.
32. SALAM A.M., AL-MOUSA E.N. The therapeutic potential of ximelagatran to become the anticoagulant of choice in medicine : a review of recently completed clinical trials. *Expert. Opin. Pharmacother.*, 2004, **5** : 1423-30.