REVIEW

Resistance to activated protein C – frequent etiologic factor for venous thrombosis

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Abstract

The discovery of the resistance to activated protein C (APCR) has provoked a new insight into the etiopathogenesis of venous and arterial thrombosis. APCR is determined in 95 % genetically by point mutation in the gene for factor V resulting in substitution of arginine in the position 506 by glutamine. This change makes the activated form of factor V (factor Va) resistant to the cleavage by protein C in the place, where the cleavage takes place most quickly under normal conditions. The mutant factor V is known as factor V Leiden. Factor V Leiden preserves its procoagulation activity for a longer period, resulting thus into thrombophilia with all its negative consequences.

The inherited deficiencies of antithrombin III, protein C and protein S occur in 10 % of patients suffering from venous thrombosis, whereas factor V Leiden is present in as many as 20 to 60 %. Thus, it seems that factor V Leiden is the most important inherited risk factor of venous thrombosis.

The results of several trials did not indicate the participation of APCR in the development of myocardial infarction. On the other hand, APCR seems to be a risk factor of cerebrovascular accidents, especially of stroke and transitory brain ischemia. Factor V Leiden is an important risk factor of abortions, especially those occuring in the second trimester of pregnancy. According to recent results, factor V Leiden is considered to play a role in the pathogenesis of venous and arterial thromboses in children.

The significant risk potential of factor V Leiden with respect to venous thrombosis development and relatively simple diagnosis of this mutation predispose the investigation of this disorder to become the screening method in indicated groups of patients. The investigation of APCR is recommended in all patients with either first or reoccuring attacks of venous thrombosis or thromboembolism, in patients with positive family history of thrombosis and thromboembolism and in women with repeated abortions, particularly in the second trimester of pregnancy. The investigation of APCR in selected groups of patients and early prophylactic anticoagulation therapy may be important in thrombosis prevention in situations with an increased thrombotic potential. ***(Tab. 1, Ref. 78.)***

Key words: thrombosis, APCR, factor V Leiden.

Venous thrombosis and thromboembolic attacks represent serious health and social problems (1). According to the frequency of their occurrence, they rank to the third place, immediately after acute myocardial infarction and stroke (2). The incidence of venous thrombosis and thromboembolism is 1 case per 1000 people and these diseases represent an important cause of cardiovascular morbidity, and morbidity per se (3).

The conditions predisposing venous thromboses are called hypercoagulation states (thrombophilia). The term thrombophilia was used for the first time by Egeberg in 1965 in association with one family, in which the genetically determined shortage of antithrombin was linked with an increased incidence of thromboses (4).

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Alterations in blood composition are supposed to be present in thrombophilia, which results in blood clotting upon stimuli which do not induce the clotting in normal blood. Thrombophilic states can be divided into inherited or acquired (Tab. 1).

Thromboses determined by inherited thombophilia have particular characteristics: 1. young age at onset; 2. recurrent course; 3. atypical, often migrating localisation; 4. often unclear etiology, and manifestation after minimal stimuli; 5. strongly positive family history (5, 6).

The states associated with familial thrombophilia are represented by thrombophlebitis, posthrombophlebitic syndrome, venous ulceration of the pretibial area, mesenteric and cerebral thromboses, thrombosis of lower extremities, pulmonary embolism, but also such states as warfarin induced skin necrosis, neonatal purpura fulminans and increased risk of abortions. The most important manifestation of inherited thrombophilia is represented by venous thromboses.

The most frequent genetically determined abnormalities leading to familial thrombophilia are the resistance to activated protein C, deficiency of antithrombin III, protein C and protein S, and mutation of prothrombine A20210G (7).

Tab. 1. Thrombophilic states.

A. Inherited thrombophilia
Common:
Resistance to activated protein C
Deficit of antithrombin III, of protein C and of protein S
Mutation of prothrombin A20210G
Less common:
Dysfibrinogenemia
Deficit of heparin II cofactor
Deficit of Hageman factor
Abnormal Hageman's factor
Abnormal thrombomodulin
Disorders of fibrinolytic system
B. Acquired thrombophilia
Antiphospholipid antibodies: lupus anticoagulants
cardiolipins antibodies
malignancies
immobilisation
right heart failure
vein varices
postthrombophlebitic syndrome
collagenoses
pregnancy and puerperium
oral contraceptives

Resistance to activated protein C (APCR)

The resistance to activated protein C (APCR) is determined by an abnormality in the molecule of factor V, which determines an insufficient response of the activated form of factor V (factor V a) to the proteolytic effect of activated protein C (APC).

The genetic defect causing APC-resistance is a single point mutation in the factor V gene; at the nucleotide position 1691, guanine is substituted with adenine. This mutation leads to the replacement of arginine at the amino acid position 506 with glutamine (8, 9, 10). The mutant factor V (factor V Leiden) is resistant against the cleavage by activated protein C in positions 306 and 679. Consequently, the cleavage takes place, however it is less rapid. This disturbance causes that the factor V remains in its procoagulation activity for a longer period. It can result in increased thrombin formation associated with the hypercoagulative state — thrombophilia (11, 12).

The factor V Leiden is present in 95 % of patients with APCR (8, 13). The inheritance of factor V Leiden is autosomally dominant, with variable expressivity (8, 16). Heterozygous carriers of this mutation have, compared to normal population, a 5 to 10 times increased risk of venous thrombosis, while in homozygotes it is increased as much as 80 times (8, 16). When compared to homozygotes, heterozygotes develop thromboses at younger age (the median is 31 years in homozygotes and 47 years in heterozygotes). Thromboses are associated with embolisation and often arise without any discernible cause. Patients with factor V Leiden have higher incidence of recurrent thromboses than patients with the deficiency of antithrombin III, or protein C and protein S. The incidence of thromboses in homozygous carriers of factor V Leiden is higher than in heterozygotes (16).

The occurrence of factor V Leiden in the population varies between 0—15 % (17). It has a certain geographic dependence. Within the European population, it varies between 0—7 % (14). A 2 % occurrence was observed in the Netherlands, 3.2 % in Germany, 4.4 % in the United Kingdom. In natives of Australia, America, Africa, and Asia, factor V Leiden does not occur (18). In the Czech Republic and Slovakia, the prevalence of APCR is about 3.2 %. (19).

Clinical picture of APCR

APCR, as an inherited thrombophilic state, is an important risk factor increasing the potential of thrombotisation. In patients with APCR, the clinical manifestation was similar to that observed in patients with the deficiency of protein C, protein S, antithrombin III or hyperprothrombinemia determined by mutation of the gene encoding prothrombine formation G20210A (13, 14). The most frequent clinical disorders in APC resistant patients are deep venous thromboses and pulmonary embolism, the latter being less frequent (2, 20). The investigation of APCR in patients with thromboses (especially of lower extremities) proved a 20 to 60 % prevalence of factor V Leiden (14, 15, 21). It seems that APCR is the most frequent inherited factor of thrombotisation (14).

Thromboses may arise seemingly in a spontaneous way, without any discernible cause (the triggering factor being the older age). However, most thromboses arise in connection with other risk factors which are as follows: surgical interventions, immobilisation, pregnancy and puerperium, usage of oral contraceptives etc. (5, 22, 23, 24, 25). These factors represent risk situations which, in patients predisposed to thromboses on the base of APCR, increase the risk of thrombotisation. These factors often act as the triggering factors of thrombotisation, and their simultaneous occurrence with APCR should lead to increased antithrombotic prophylactic vigilance (5, 25).

The high prevalence of factor V Leiden in the population enables a parallel occurrence of this factor with other disorders of anticoagulative proteins, especially with the deficiency of antithrom-

bin III, protein C and protein S, and with the mutation of prothrombine G20210 (6, 12, 26, 27, 28, 29). In the families with the concomitant occurrence of factor V Leiden and protein C deficiency, thromboses were observed in 31 % of individuals with isolated deficiency of protein C, in 13 % with factor V Leiden, and in as many as 73 % of individuals with both abnormalities (30, 31, 32). Similarly, thromboses were described to occur increasingly in the cases of combination of factor V Leiden with the deficiency of antithrombin III, where they were observed in 72 % of carriers of these genetical abnormalities (34). The frequency of thromboses in cases with both, factor V and mutation of prothrombin G20210A, has not been mapped precisely till now (13, 28). It is obvious, however, that the presence of both genetical abnormalities increases the risk of origin of venous thromboses (13).

Thus it seems clear that patients with combined occurrence of anticoagulation disorders suffer from an increased risk of thrombosis when compared to patients with an isolated disorder (12, 13, 28, 32). The risk of thrombotisation in patients with APCR increases not only in association with external risk factors of thrombotisation, but also in combination with other genetically determined defects of the anticoagulation system (18, 29).

APCR in newborns and children

The thromboembolic disease is a relatively seldom cause of morbidity and mortality in newborns and children. Especially two facts seem to be responsible:

— the formation of thrombin in children is by 20 to 50 % slower than in adults (35),
— the most important factors of thromboembolism — pregnancy, oral contraceptives, prolonged immobilisation, surgical interventions and malignancies are typical for adults and are almost not present in children (36).

The counterpart to this natural antithrombotic potential in children seems to reside in the fact that although the levels of factor V and VIII in plasma in children and newborns are comparable to those in adults, the protein C and protein S levels are lower. Thus the capacity of protein C to inactivate the factor Va in children is decreased (35). It is clear that the mutation of factor V — factor V Leiden — contributes further to the already restricted anticoagulation capacity of protein C, thus increasing the risk of thrombosis (36). With respect to the presented facts it can be supposed that factor V Leiden is a risk factor also in children. Its prevalence in children with venous thromboses is comparable to the prevalence of factor V Leiden in adults, and varies between 20 to 40 % (36).

Despite the fact the factor V Leiden in the adult population is not unequivocally proved to participate in arterial thrombosis, it seems that this factor could play a substantially more important role in newborns and children (36, 37, 38, 39). Factor V Leiden and protein C deficiencies were observed in as many as 60 % of children after vascular brain accident (38).

It is known that several issues participate in the development of intracranial bleeding in newborns. In addition to generally accepted risk factors as prematurity, asphyxia and acidosis, also hypercoagulation states are supposed to play a potential role. Hypercoagulation can result in intracranial vascular occlusion with subsequent intracranial blood increase in terminal veins causing their rupture and haemorrhage (40). In newborns with intracranial bleeding, the occurrence of factor V Leiden was 2.5-times higher than in asymptomatic newborns (40). The confirmation of the importance of factor V Leiden in the pathogenesis of intracranial bleeding would not only mean a new insight in to the patomechanism of intracranial bleeding but would probably induce a new approach to potential preventive interventions hindering the thrombosis development in these children.

APCR and pregnancy

Thromboembolic complications rank to the most frequent causes of morbidity and mortality in pregnancy (41). They are a serious threat for both mother and child.

The changes in the hemocoagulation system of pregnant women minimise the risk of blood losses, however, they can simultaneously increase the risk of thromboembolic complications. The reason of this phenomenon is still not quite clear. It is proved, however, that during pregnancy, the coagulation system increases its activity, and the protein C system and fibrinolysis are inhibited (42). The use of oral contraceptives provokes similar changes in the coagulation system (23, 43).

Due to the above reasons, the pregnancy is considered to be a state of chronically compensated intravascular coagulation (41), in which even minimal, often subclinical dysfunctions of the hemocoagulation-trombolytic system may induce serious clinical problems.

The frequency of thrombosis occurrence in pregnancy is higher in the cases with shortage of antithrombin III, protein C and protein S (44, 45). Deficiencies of antithrombin III, protein C and protein S were proved only in 4 % of patients with thrombotic complications in pregnancy, and due to this reason no important role of these disorders is supposed in the pathogenesis of thrombosis in relation to pregnancy (46). On the other hand, however, APCR was proved in 55—60 % of women suffering from thromboses during pregnancy (23, 24, 47) and therefore it is considered to be an important risk factor of venous thromboses in pregnant women.

Reoccurring abortions are considered to be the most important consequence of APCR during pregnancy. They pertain to the group of gynecologic diseases, the etiology of which is not exactly elucidated. In addition to particular anatomical, endocrine, infectious and imunological disorders, also hypercoagulability of blood and concomitant placental thrombosis are considered to be important etiologic factors. The presence of antiphospholipid antibodies, the deficiency of factor XI, and the depression of thrombolysis in patients with reoccurring abortions support the theory of the participation of disorders of coagulation parameters in the etiopathogenesis of abortions (47, 48).

The increased incidence of factor V Leiden in patients with reoccurring abortions was described by several authors (47, 48, 49). The prevalence of factor V Leiden was 20 % in women with abortions in the second trimester, while only 5.7 % in women with abortions in the third trimester. It is supposed, that factor V Leiden is an important risk factor of abortions especially in the second trimester of pregnancy and much less important in the third trimester. Several authors (47, 50, 51, 52) recommend to investigate APCR in all women with abortions in the second trimester.

Wiener-Megnagi et al. (53) observed a 30 % prevalence of factor V Leiden in the group of women with abruption of placenta, and therefore they recommended to investigate factor V Leiden also in patients with this diagnosis. The latest studies lay stress on the possible relation between APCR determined by factor V Leiden and hypertension in pregnancy (52).

Other states associated with APCR

APCR and surgical interventions

APCR increases the risk of thrombotisation in association with other risk factors. Undoubtedly, surgical interventions represent important risk situations, especially when operation is linked with prolonged immobilisation. In the case of parallel occurrence of APCR and surgical intervention, two prothrombotic factors are cumulated, and the risk of thrombotisation increases (54).

APCR and various localisations of venous thrombosis

It is generally accepted that disorders of the coagulation system participate in the pathogenesis of cerebral venous thromboses. In approximately 25 % of cases, the reason remains obscure. The association of factor V Leiden with these thromboses has been followed since 1994, when factor V Leiden was discovered. The results of clinical studies revealed that factor V Leiden is an important risk factor of both cerebral venous thromboses and their reccurrence (55).

Recent studies have confirmed the participation of factor V Leiden in the etiopathogenesis of thromboses of portal and mesenteric veins, and also in those of vena cava inferior, especially in cases with unclear etiology. Factor V Leiden occurs relatively often in Budd-Chiary syndrome, while clinical manifestation of this disease occurs mostly when factor V Leiden is combined with other risk factors (56). On the other hand, factor V Leiden in not considered to be a risk factor of renal vein thrombosis in patients with nephrotic syndrome (57), or of thromboembolic complications in patients with inflammatory bowel diseases such as Crohn disease and ulcerous colitis (58).

APCR and arterial thrombosis

Although the idea of the association of increased myocardial infarction incidence in particular families or areas with inherited disorders of coagulation, like APCR, seems to be very attractive, the accomplished studies have not confirmed that APCR participates in the origin of myocardial infarction (59). APCR is, however, an important risk factor of cerebrovascular diseases, especially of stroke and transitory brain ischemia (59,60). However, these studies focused their investigation on APCR, and not directly on factor V Leiden. That is why the data on the participation of factor V Leiden in the stroke development are missing (59). Having in mind, however, that APCR is in 95 percent caused by factor V Leiden, the role of factor V Leiden in the origin of stroke is more than probable (60).

APCR and oral contraceptives

The risk of venous thrombotization was observed to increase 30 times in women with APCR using oral contraceptives. The results of recent SZO study (61) have proved that the risk of thromboembolism in women using oral contraceptives, is four times higher, when compared to women, who do not take oral contraceptives (62). Bearing these facts in mind, it was suggested that APCR investigation should be performed in all women with positive personal and family history of thromboses and thromboembolism before starting the treatment by oral contraceptives (43, 62).

Acquired forms of APCR

From 5 to 10 % of cases of APCR are determined by factors different from factor V Leiden (18, 63).

Several studies yielded evidence that lupus antibodies caused the acquired form of APCR. These antibodies represent a large group of protein substances which can interfere with the reaction in the system of protein C, thus causing APCR (64, 65, 66, 67).

The inhibition of thrombolysis, increased activity of hemocoagulation, and inhibition of protein C are a part of physiologic adaptive changes during pregnancy. Thus, some authors suppose that acquired APCR may be linked with pregnancy (24). Cumming et al. (68) observed the development of APCR in 42 % of women between 14th to 20th week of pregnancy, and up to 55 percent in 28th week. It is not clear, however, whether the APCR which had developed in these women was in causal relationship with thrombosis in pregnancy (18).

It has been shown that the response of protein C is attenuated during treatment by oral contraceptives, the fact of which may be related to changes in levels of coagulation factors (42, 69, 70, 71).

Diagnostic of APCR

Diagnosis of APCR should be based on the consideration of mutual interdependence between the clinical picture, anamnestic data and laboratory investigation of APCR.

The most frequent laboratory test used for the determination of APCR is the APCR ratio based on the measurement of two APTT reactions during the presence and during the absence of an exactly determined amount of APC (standardised amount of APC).

$$\frac{\text{APTT + APC}}{\text{APPTT (without APC)}} = \text{APCR ratio}$$

APCR ratio higher than 2 indicates APC resistance.

In order to achieve comparability of data acquired by the above method among different laboratories, APCR is normalised against the referent APCR ratio of normal plasma (nAPCR ratio) (73).

$$\frac{\text{APCR ratio of patient}}{\text{Reference APCR ratio of normal plasma}} = \text{normalised APCR ratio (nAPCR ratio)}$$

APCR is considered to be a state, when nAPCR ratio is lower than 0.84. The sensitivity and specificity of this method varies between 85 to 90 % (26). The results gained by the described method are influenced in considerable measure by other factors, which can interfere with APCR, particularly factor VIII, protein C and protein S, lupus antibodies and the using of oral contraceptives (66, 72, 73).

In order to minimise the restriction of this method, a modified test has been developed. It is based on the dilution of patient's plasma in plasma with the deficit of factor V (74, 75). Alternatively an amidolytic method can be used. It is an exclusive method appropriate during the anticoagulant treatment (27). The amidoly-

tic method is more sensitive and specific to factor V Leiden. Its specificity and sensitivity is about 100 %; that is why it is convenient as a screening test of APCR (74).

The modified test is exclusively able to detect APCR caused by factor V Leiden (5, 76), whereas normalised APCR ratio covers also APCR determined by other factors. Respecting that, both tests should be performed in the precise diagnosis. APCR proved by the given methods should be confirmed also by genetic analysis of factor V (18).

The fact that 90 to 95 % of patients with APCR phenotype are carriers of factor V Leiden (mutation G1691A), along with the variable validity of the previously described methods, support the view that the investigation of factor V genotype should be recommended. This method is quick and precise. It has 100 % specificity and sensitivity to factor V Leiden, and enables to differentiate unequivocally the homozygous form of mutation from the heterozygous one. Considering the nature of mutation (simple point mutation), the PCR analysis of factor V Leiden seems to be an optimal method (27, 77).

PCR analysis of factor V Leiden

The PCR analysis consists of splitting and manifold amplification of 267 pairs of bases of the long DNA sequence of the factor V gene with subsequent splitting by the specific enzyme Mnl, which has to decide, whether the allele in the position 1691 is normal (guanine) or mutated. The cleavage of 267 pairs of bases of the long sequence of DNA to fragments with the length of 37, 67, and 167 pairs of bases indicates guanine in the position 1691 representing the normal finding.

The cleavage of DNA to fragments with the length of 67 and 200 pairs confirms adenine in the position 1691 representing the normal finding (8). The cases, in which, in addition to 67 and 200 pairs of long fragments, also the withdrawal of fragments with 37 pairs takes place, indicate the homozygous mutation. The cases of withdrawal of 37, 67, 167 and 200 pairs of bases of long fragments indicate the presence of the heterozygous mutation (8).

Having in mind the high specificity and sensitivity of the genetical analysis of the factor V Leiden and the unique ability of this method to differentiate homozygous and heterozygous mutations, genetic analysis could be introduced as a screening test (26).

On the base of the given facts, the PCR analysis of factor V Leiden should be indicated in following situations (78):

— patients with overridden and reoccurring venous thrombosis or thromboembolism,
— persons with positive family history of thromboses and tromboembolisms,
— women with abortions in the third and especially in the second trimester of pregnancy (78).

Therapy of APCR

Despite the discernible improvement of diagnostic approaches to the detection of APCR, the treatment has not yet been exactly standardised. The decision on starting the treatment should be based on a thorough consideration of the clinical picture, personal history, as well as the family history of the patient.

The pregnancy in patients with APCR is an indication for microheparinisation. Women using cumarin anticoagulants should be, respecting the teratogenic effects of cumarins, transferred to heparin, in case that pregnancy is confirmed. It is recommended to continue the heparin therapy 6 to 8 weeks after childbirth (78). APCR is an indication for preventive microheparinisation also before planned operations.

The evidence of prothrombotic abnormality in the coagulation system and personal history of thromboembolic attacks is an absolute contraindication for oral contraceptives. This fact along with the knowledge that the risk of thrombotisation in APCR positive patients taking oral contraceptives is increased from 6 to 8 times, should lead to an individual approach in the prescription of oral contraceptives respecting other possibilities of contraception (25, 63).

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Abstrakt

Šimková M., Šimko F., Kovács L.:
Rezistencia na aktivovaný proteín C — častý etiologický faktor venóznych trombóz
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Objav rezistencie na aktivovaný proteín C (APCR) priniesol nový pohľad na etiopatogenézu venóznych aj arteriálnych trombóz. APCR je v 95 % prípadov podmienená geneticky, a to bodovou mutáciou v géne pre faktor V, ktorá spôsobuje substitúciu arginínu v pozícii 506 glutamínom. Táto zmena má za následok, že aktivovaná forma faktora V (faktor Va) je rezistentná proti štiepeniu proteínom V v mieste, kde štiepenie za normálnych okolností prebieha najrýchlejšie. Faktor V si tak ponecháva svoju prokoagulačnú aktivitu dlhší čas, čo vedie k trombofílii so všetkými negatívnymi následkami uvedeného javu. Mutovaný faktor V sa nazýva faktor V Leiden.
V pacientov s venóznymi trombózami sa vrodený deficit antitrombínu III, proteínu C a S vyskytuje v 10 %, kým faktor V Leiden až v 20—60 % prípadov. Zdá sa preto, že faktor V Leiden je najvýznamnejším vrodeným rizikovým faktorom venóznej trombotizácie.
Výsledky viacerých štúdií nedokázali účasť APCR na vývoji infarktu myokardu, APCR je však rizikovým faktorom cerebrovaskulárnych príhod, predovšetkým náhlej cievnej mozgovej príhody a tranzitórnej mozgovej ischémie. Faktor V Leiden je významný rizikovým faktorom abortov predovšetkým v II. trimestri gravidity. Novšie sa predpokladá účasť faktora V Leiden na etiopatogenéze venóznych a arteriálnych trombóz aj detského veku.
Významná rizikovosť faktora V Leiden v súvislosti s venóznymi trombózami a pomerne jednoduchá diagnostika tejto mutácie upozorňujú na význam zavedenia skríningového vyšetrenia v indikovaných skupinách pacientov. Vyšetrenie APCR sa odporučuje u všetkých pacientov s prekonanou a recidivujúcou venóznou trombózou, prípadne tromboembóliou, u pacientov s pozitívnou rodinnou anamnézou na trombózy a tromboembólie a u žien s opakovanými potratmi predovšetkým v II. trimestri gravidity. Vyšetrenie APCR vo vybraných skupinách pacientov a včasné začatie účinnej profylaktickej antikoagulačnej terapie má veľký význam z hľadiska prevencie trombóz v situáciách, ktoré sú známe ako tromboticky rizikové. *(Tab. 1, lit. 78.)*
Kľúčové slová: venózne trombózy, APCR, faktor V Leiden.

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