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Research Article

Hypercoagulability and Ischemic Stroke in Young Patients

Healthcare

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Ilirjana Zekja		**University Hospital Center "Mother Theresa" Service of Neurology, Tirana, Albania.**
Silvana Mijo		**University Hospital Center "Mother Theresa" Service of Neurology, Tirana, Albania.**
Eliverta Konda		**University Hospital Center "Mother Theresa" Service of Neurology, Tirana, Albania.**
Stela Muça		**Faculty of Technical Medical Sciences, University of Medicine, Tirana, Albania.**
Mira Rakacolli		**University Hospital Center "Mother Theresa" Service of Neurology, Tirana, Albania.**
Jera Kruja		**University Hospital Center "Mother Theresa" Service of Neurology, Tirana, Albania.**

Abstract

Introduction: Hypercoagulable states have been reported as a predisposing factorfor ischemic stroke, especially among young patients. This may haveimplications on therapeutic management and secondary prevention. We have studied the frequency of prothrombotic abnormalities in young patients with ischaemic stroke, as other classic risk factors are less common in this group. Materials and methods: All patients under 50 with ischemic stroke admitted to the Service of Neurology from January 2010 through June 2011were studied. We analysed risk factors, including the presence of hypercoagulable states, and outcome. These patients were prospectively studied. The ESO 2008 diagnostic criteria for ischemic stroke are used. Titration of natyral anticoagulants was done 7 ± 2 days after cerebral infarction. Besides the routine tests, the following activity tests were performed: protein C, Protein S, homocysteinemia and antithrombin titration. Results: We included 36 patients,under 50 years of age, diagnosed with cerebral infarction of undetermined cause randomly presented to the University Service of Neurology January 2010 – June 2011. There were 16 males (44.4%) with a mean age of 30 years old (23 - 48). The mean age for 20 females (55.6%) was 28 years old (22 - 45). 1 patient (2.7%),hadantithrombin deficiency. Isolated protein S deficiency was detected in 5 cases (13.8%); in 1 case we observed the association between protein S deficiency and antiphospholipid antibodies; protein C deficiency was seen in 2 case (5.5%). Conclusions: The hypercoagulable states are common in young patients with ischaemic stroke, so we recommend the screening for hypercoagulable states in all young patients with ischemic stroke.

Introduction

Thrombosis is in the core of the pathological physiology of ischemic stroke. The thrombosis is secondarily activated, following a vascular pathology in most cases, but ischemic stroke may be the consequence of primarily disorders of hemostatic mechanisms, in a part of them, as well. Consequently the undiserable thrombus formation can happen in the cerebral circulation. In this context, there has been defined an interactive system, functioning between the cell and fluid components of hemostasis, and in this system is found to be in balance the inhibitory and excitatory coagulation factors.

The main factors of this system, are:

1. The platelets;
2. The coagulation factors and their inhibitors;
3. The fibrinolytic system;
4. The vascular endothelium.

The Coagulation Factors and their Inhibitors

There are a few factors and co-factors interacting between each other in the coagulation system, throughout which the thrombin effect consists on transformation of fibrinogen in insoluble fibrin from a soluble protein precursor. There is evident an important role of thrombin in hemostasis system, because it is one of the

most important platelets agonists, and it plays an excitatory effect in an anticoagulant natyral system (protein C – protein S –thrombomoduline system). The final path of forming thrombin by prothrombin, include the formation of an excitatory complex with Ca for the Xth and Vth factor of coagulation. It happens in a phospholipid surface of activatet platelets. The final common pathway, bounds together the intrinsic coagulation system activated from the surface contact and the extrinsic system, activated from the tissue factor release (thromboplastyn). As the result of coagulation and platelet activation, a hemostatic cap is formed, consisting of aggregated platelets and fibrin.

The Coagulation Inibitors

The physiological inhibitory mechanisms, oppose the uncontrolled fibrin formation. They are set three most important coagulation inhibitors: the antithrombin (known before as antithrombin III); the protein C; and the protein S (the protein C cofactor). The antithrombin III is a seric proteases inhibitor, whose action is focused against XIIa, XIaandIXain the extrinsic coagulation path. Its inhibition effect is empowered from the glucosaminoglycans (heparin – like molecules), as well as from heparin given for therapeutic goal. The activated protein C, inhibits the activated coagulation factors VIIIa and Va. The protein S is very important for the protein C activity, functioning as a protein C cofactor. On the other hand, the thrombin and thrombomodylin are very important in the protein C activation, as endothelderivant cofactor.

The Fibrinolysis

The fibrinolyticmechanism provides a further control on thrombus formation process. The plasmin formed under the effect of plasminogen activated factor (t-PA), can dissolve the fibrin into a solublefibrinolytic degradation product. The fibrinolytic process is modulated by the interaction between the excitatory and inhibitory coagulation factors in the coagulation system.

Hemostatic Mechanisms

Disorders and the Trombosis It is identified a sure and clear link between the coagulation mechanisms and occlusive arterial disease, including even the stroke. The hemostatic mechanisms are as included in the evolution and progression of the atheromas, as important for platelet / fibrinotyc thrombus during the acute phase of occlusive event. Prothrombotyc condition is defined as a special situation, with multifactorial causes / mechaisms.In specific way, some of these conditions determine as hemostatic disorders are clearly related with a high thrombotic risk. Below are listed some of these conditions:

1. Congenital trombophylia – it is caused by the deficiency of a natyral anticoagulation factor (Protein C, protein S, orantithrombin);
2. Acquired disorder = the primary antiphospholypidsyndrom (it is in relation with the presence of autoantibody towards phospholipid, and this is accompanied by high thrombotic risk);
3. Myeloproliferativediseases: essential thrombocytemi and & polycytemiaverae (thrombocytosis with/out high platelet reactivity, is in the base of high thrombotic tendency).

Congenital Trombophylia

There are identified the most important and frequent disorders of hemostatic control mechanisms, that predispose for thrombosis, as below: 1. The antithrombin III deficiency; 2. Protein C deficiency; 3. Protein S deficiency. It was discovered on 1965 the correlation between the thromboembolism and hereditary deficiency of antithrombin III (O. Egeberg 1965: Inherited antithrombin III deficiency causing thrombophilia). The

antithrombin III deficiency, with the prevalence 1/20 000 – 1/40 000, is found to be responsible for 2 – 5 % of venous thromboembolism. These thrombotic events are rare in children, but the thrombotic risk for persons 15 – 30 years, is estimated to be almost 65% (J. Hirsh & Co 1989: Congenital antithrombin III deficiency). The protein C and protein S are vitamin K dependent protein. The hereditary deficiency of protein C and S are described for the first time on 1981(JH Griffin & Co 1981: Deficiency of protein C in congenital thrombotic disease), and 1984 (PC Comp & Co 1984: Familial protein S deficiency associated with recurrent thrombosis). The prevalence of protein C deficiency is undefined, but in healthy blood donors it is found 1/200 persons (JMiletich 1987: Absence of thrombosis and subjects with heterozygous protein C deficiency). The symptomatic deficiency is rarer, and it is found to be 1/36 000 individë (CL Gladson 1988: The frequency of type I heterozygous protein C deficiency in 141 unrelated young patients with venous thrombosis). Based on the above figures, we can say that heterozygote condition may be clinically silent. The homozygote conditions are more often associated with life threatening thrombosis (ATripodi 1990: Asymptomatic homozygous protein C deficiency). The plasmatic protein S is free in circulation. It"sfree state, may play the cofactor role for the activated protein C. The most frequent protein S deficiency is a heterozygous condition, in which there are very low levels of free protein S , and almost all this amount of protein S is bounded by its binding protein C4bBP (C4b binding protein). There are so rare the conditions in which as levels of fraction of free protein S, as level of bounded protein Sare reduced. The protein S deficiency has almost the same thrombotic risk as protein C deficiency (L Engesser1987: Hereditary protein S deficiency, clinical manifestations).

Results

We included 36 patients, under 50 years of age, diagnosed with cerebral infarction of undetermined cause randomly presented to the University Service of Neurology fromJanuary 2010until June 2011.These patients were prospectively studied. The ESO 2008 diagnostic criteria for ischemic stroke are used. We analysed risk factors, including the presence of hypercoagulable states, and outcome. Titration of natyral anticoagulants was done 7 ± 2 days after cerebral infarction. Besides the routine tests, the following activity tests were performed: protein C, Protein S, homocysteinemia and antithrombin titration. We didn't use patients stratification based on ischemic lesion localization. 36 patients were divided patients based on their age, using as a borderline 50 years. There were 16 males (44.4%) with a mean age of 30 years old (23 - 48) and 20 females (55.6%) with a mean age 28 years old (22 - 45). Excluding all other risk factor for ischemic stroke, we dosed antithrombin III, protein C and protein S for all these patients.

Antithrombin IIII deficiency

They were identified 1 patient (2.7%), with antitrombin III deficiency. They are a few studies referring antithrombin deficiency as correlated with ischemic stroke. One study refers 3 patients with antithrombin deficiency of 45 studied, but its mentioned to be temporary reduction (JErnerudh 1990: Antithrombin III deficiency in ischaemic stroke). In another study performed in Turkey and published on 2007 were retrospectively assessed risk factors in children with arterial stroke, were found 2 from 31 patients studied with antitrombin III deficiency (S Gokben 2007: Arterial ischemic stroke in childhood: risk factors and outcome in old versus new era). All the studies, despite the frequency of antithrombin III deficiency, included patients 45 until 55 years. (Angela Mirela Soare 2010: efficiencies of protein C, S and antithrombin and factor V Leiden and thë risk of ischemic strokes).

Protein C deficiency

In our study there were 2 patients (5.5%) with protein C deficiency. They are reported different data for protein C deficiency in different study, but we should emphasize that these patients (protein C deficiency) have stroke in younger age than other patients without that deficiency (J Hirsh 2004: Overview of thrombosis and its treatment). In another study, only one from 329 patients (15 – 45 years) have protein C deficiency. Therefore, its not a strong relation between protein C deficiency and arterial stroke (MMoster 2003: Coagulopathies and arterial stroke).

Protein S deficiency

In our study, there were 5 patients (13.8%), with protein S deficiency. In different study we found relatively high number of patients with protein S deficiency, as: 13.8% (5/36 patients), 19% (8/35 patients, 23% (19/98 patients) according to the patients age. (M. Moster2003: Coagulopathies and arterial stroke). It was supposed that these factors level decreas in acute phase of thrombtic event. Protein S level decreases notably after acute activation of complement, consequentlyit is recommended titration of Protein S after 6 months. (Martin PJ & Co 1997: Causes of ischaemic stroke in the young). Conclusions The hypercoagulable states are common in young patients with ischaemic stroke, so we recommend the screening for hypercoagulable states in all young patients with ischemic stroke.

References

1. O. Egeberg 1965: Inherited antithrombin III deficiency causing thrombophilia.
2. J. Hirsh & Co 1989: Congenital antithrombin III deficiency.
3. JH Griffin & Co 1981: Deficiency of protein C in congenital thrombotic disease.
4. PC Comp & Co 1984: Familial protein S deficiency associated with recurrent thrombosis.
5. J Miletich1987: Absence of thrombosis and subjects with heterozygous protein C deficiency.
6. CL Gladson1988: The frequency of type I heterozygous protein C deficiency in 141 unrelated young patients with venous thrombosis.
7. A Tripodi1990: Asymptomatic homozygous protein C deficiency.
8. L Engesser1987: Hereditary protein S deficiency, clinical manifestations.
9.J Ernerudh 1990: Antithrombin III deficiency in ischaemic stroke.
10. S Gokben2007: Arterial ischemic stroke in childhood: risk factors and outcome in old versus new era.
11. Angela MirelaSoare 2010: efficiencies of protein C, S and antithrombin and factor V Leiden and thë risk of ischemic strokes.
12. J Hirsh 2004: Overview of thrombosis and its treatment.
13. M Moster2003: Coagulopathies and arterial stroke. 14. Martin PJ & Co 1997: Causes of ischaemic stroke in the young.