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ORIGINAL RESEARCH

Elevated factor VIII level and stroke in patients without traditional risk factors associated with cardiovascular diseases

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Introduction: Hemostasis is affected by interactions between physiological processes, including those connected with the coagulation system, whose essence is converting fibrinogen into fibrin. The role of factor VIII (FVIII) consists in activating factor X, which directly participates in the generation of thrombin, which is able to produce stable fibrin, which in turn forms blood clots. There are divergent opinions regarding the significance of high levels of FVIII in stroke pathogenesis.

Aim: The aim of our study was to evaluate FVIII activity in individuals with cryptogenic stroke in order to determine a potential relationship between it and cerebral ischemia.

Material and methods: Nine patients suffering with stroke were used in this study: six women and three men aged 49–63 years. In all of the patients, the presence of known and potential risk factors for stroke had been excluded during previous diagnostic procedures. These patients accounted for 1.2% of the 719 people who suffered a stroke and were hospitalized in 2011 at the Stroke Unit. FVIII activity was examined in each of the nine qualified subjects within 1–2 months of the occurrence of stroke (the first test) and repeated (the second test) in five patients with abnormal results obtained from the first examination.

Results: Increased activity of FVIII was found in 5 out of 9 patients. In patients with abnormal results, elevated FVIII was found in follow-up examinations in the 8th–10th month following stroke. Hemodynamic abnormalities in carotid or cerebral artery (presence of thrombus) were found in 3 of the 5 patients with increased FVIII levels. In the first 24 hours following stroke the neurological state of patients with abnormal FVIII was worse than individuals with normal FVIII activity. The patients with abnormal FVIII levels were found to be more disabled in the examination of self-dependence on the 90th day after stroke.

Conclusion: When searching for the causes of stroke, it is worth examining the coagulation system, including FVIII concentration, the abnormality of which may play a significant part in brain ischemia. More research is needed to determine the relationship between abnormal FVIII activity and stroke.

Keywords: factor VIII, cryptogenic stroke, hemostasis, risk factor

Introduction

Hemostasis is affected by interactions between physiological processes, including those connected with the coagulation system, the essence of which is converting fibrinogen into fibrin. More than ten factors participate in the process of fibrin production; most of them circulate in plasma in the form of inactive proenzymes, which are activated by cofactors.

Factor VIII (FVIII), a β_2-globulin, produced in the liver, spleen and lymph nodes, consists of 6 subunits (A1-A2-B-A3-C1-C2) and 2 chains (a light and a heavy one).[1] In the plasma, 95% of its molecules circulate in a complex with von Willebrand factor

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(vWF), which protects it from inactivation by protein C, increasing its half-life.[2] The role of FVIII consists in activating factor X, which directly participates in the generation of thrombin that is able to produce stable fibrin which is needed to form clots. Decreased FVIII occurs in patients with hemophilia type A, von Willebrand disease, liver damage, treated with valproic acid, drinking alcohol and in individuals with blood group O.[3] Low FVIII levels impair the production of fibrin due to an insufficient amount of substrate for reactions activating factor X, which is necessary in the process of converting fibrinogen into fibrin.

It has been observed that hemophilia A is associated with significantly decreased cardiovascular morbidity and mortality. In 1990, Rosendaal published the results of the observation of 90 Danish families with hemophilia. The research subjects suffered significantly less often from coronary artery disease (CAD) and myocardial infarction (MI) despite the fact that arterial hypertension occurred more commonly in them than in the general population.[4] In the material collected by Sramek et al, a reduction in all-cause mortality by 22% and in CAD mortality by 36% was observed in FVIII gene mutation carriers (the mothers of hemophiliacs).[5] The results of the above studies suggest that FVIII participates in the pathogenesis of arterial thrombosis. However, opinions in this matter are divergent, though they agree that high levels of FVIII increase the risk of venous thrombosis.[6–9] Arterial thrombi, in comparison with venous ones, mostly consist of platelets, and the amount of fibrinous stroma is lower.[10] It is estimated that the etiology of arterial thrombosis is unknown in almost half of all cases.[11]

The significance of the coagulation system in the pathogenesis of stroke raises no doubts. However, as the results of studies suggest, the cause of the disease is unknown in as many as 30% of cases. When determining the causes of stroke, especially in young victims unassociated with traditional risk factors, it is worth considering the examination of the coagulation system when searching for abnormal activity of prothrombotic factors.

Aim

The aim of our study was to evaluate FVIII activity in individuals with cryptogenic stroke in order to determine a potential relationship between it and cerebral ischemia.

Material and methods

Nine patients qualified for this study: six women and three men aged 49–63 years. All patients suffered from stroke of unknown cause in the previous 2 months.

In all patients, the presence of known and potential risk factors for stroke (arterial hypertension, diabetes mellitus, lipid metabolism disorders, cardiac dysrhythmia, patent foramen ovale, cardiac septal defects, connective tissue diseases, antiphospholipid syndrome, protein C, S and antithrombin abnormalities; factor V and prothrombin gene G20210A mutations) had been excluded previously during diagnostic procedures. Inflammatory and atherosclerotic diseases as well as dissections of carotid and cerebral vessels were excluded. Fibrinogen, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), international normalized ratio (INR), partial thromboplastin time (PTT), homocysteine levels and complete blood count were normal. There were no signs of liver damage, acute or chronic infections and oncological comorbidities in our patients. They denied having surgical procedures and serious traumas over the previous year. They had also not used steroid therapy.

Neuroimaging examinations (computed tomography [CT] and/or magnetic resonance imaging [MRI]) confirmed the presence of recent ischemic foci responsible for the occurrence of neurological symptoms. In the study group: four patients had carotid or cerebral artery stenosis in Doppler ultrasound examination and one patient had a decrease of blood flow velocity in the cerebral artery. Abnormalities were found in the arteries responsible for circulation in the ischemic area.

The examination of factor VIII activity (FVIII:C) was performed on all the subjects within 1–2 months of the occurrence of stroke (the first test) and repeated (the second test) on five patients with abnormal results obtained in the first examination.

The FVIII:C was determined with the use of the one-level method as a modification of activated partial thromboplastin time (aPTT). The assays were carried out with a BCS XP hemostasis analyzer (Siemens, Germany), using FVIII deficient plasma (Siemens, Germany) and Actin FS (Siemens, Germany). A percentage of the activity is calculated from the calibration curve. A calibration curve is determined based on a plasma reference (Standard Human Plasma) with a known concentration of FVIII.

Patients according to FVIII results were divided into 2 groups: I – patients with two incorrect results and II (reference group) – with only one incorrect result. The selected parameters (National Institutes of Health Stroke Scale – NIHSS and Doppler examination in the first 24 hours of stroke, Rankin scale on the 90th day following stroke) were analyzed between groups.

Results

The clinical characteristics of the patients are presented in Table 1.

Table 1 The clinical characteristics of the patients participating in the study

No	A	G	TCD/CDD/Angio	FVIII-1	FVIII-2	NIHSS	Rankin 3-month	Follow-up (month)
1	59	F	ips MCA stenosis	232.9%	–	20	3	18
2	46	F	Normal	243.0%	236.0%	10	2	16 (RIND)
3	61	F	Normal	134.3%	–	8	0	10
4	60	M	ips MCA flow depression	105.0%	–	12	4	13
5	51	M	ips ICA stenosis	275.0%	281.4%	16	4	16
6	58	M	Angiopathy without stenosis	215.2%	211.0%	10	4	12
7	50	F	Normal	125.0%	–	10	2	11
8	49	F	ips PCA stenosis	205.0%	208.6%	18	3	13
9	63	F	ips ICA stenosis	96.3%	–	18	3	10

Abbreviations: A, age; G, gender; ips, ipsilateral; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; TCD, transcranial Doppler; CDD, carotid Doppler duplex; ANGIO, angio-magnetic resonance imaging; FVIII-1, activity of factor VIII in the first examination; FVIII-2, activity of factor VIII in the second examination; NIHSS, National Institutes of Health Stroke Scale; Rankin, modified Rankin scale; RIND, reversible ischemic neurological deficit.

Increased activity of FVIII in the first examination was found in 5 out of 9 patients. In 4 patients with abnormal results, elevated FVIII was found in follow-up examinations in the 8th–10th month following stroke. One patient with an abnormal level found in the first examination did not undergo a follow-up examination for a non-medical reason. Hemodynamic abnormalities in the carotid or cerebral artery (presence of thrombus) were found in 3 of the 5 patients with increased FVIII levels (in the first examination). These incorrect parameters in Doppler procedure were more often found in individuals in group I.

The neurological state of the patients in group I in the first 24 hours of the disease was more severe in comparison with individuals from reference group. The patients from group I were found to be more disabled in a self-dependence examination taken on the 90th day following stroke.

Discussion

Increased levels of FVIII are associated with prothrombotic hyperactivity in the venous and arterial systems.[8,12,13] According to Vormittag, FVIII levels ≥232% are an independent risk of thromboembolic complications.[14] Kamphuisen suggests that FVIII levels >123 IU/dL can be the cause of 4% of all cases of arterial thrombosis.[7] The stratification of the risk of thrombosis depending on the level of FVIII is presented in Table 2.[6]

A positive correlation between an increase in the level of FVIII and the risk of exacerbation of CAD and MI was found in the Caerphilly Heart Study.[15] Similar observations have been presented by other authors.[12,16]

In the multicenter Progetto Lombardo Athero-Trombosi (PLAT) study, which included 953 patients (average age 56.1 ± 8.2 years) with ischemic events in different vascular beds, it was showed that another event (MI, stroke, and/or peripheral vascular disease) occurred in patients with elevated levels of FVIII, vWF, fibrinogen and/or with leukocytosis.[17] The FVIII-vWF complex participates in the adhesion of platelets to arterial subendothelium.[18] vWF binding to FVIII causes an increase in its concentration in the region of vessel damage. It was suggested that hemostatic factors can modify the significance of traditional risk factors for atherosclerosis and their expression in different parts of the cardiovascular system.[17]

In the theory of atherosclerosis development, activation of the plasmic coagulation system is presented as a process secondary to platelet activation.[3] The results of the Atherosclerosis Risk in Communities (ARIC) study showed a strict relationship between FVIII, vWF and traditional risk factors for atherosclerosis, such as arterial hypertension, diabetes mellitus or lipid metabolism disorders.[19] Some of them are associated with endothelial damage and the inflammatory process within the walls of vessels.[20,21]

Prospective, population-based studies show that increased levels of fibrinogen, FVII and FVIII are independent risk factors for atherosclerosis and its acute complications.[3] Thrombi, which are the cause of acute complications of atherosclerosis (limb ischemia, myocardial infarction), form on the surface of damaged atherosclerotic plaques.

Table 2 The relative risk of thrombosis depending on the level of factor VIII

FVIII:C IU/dL	Patients n (%)	Control n (%)	OR (95% CI)
<100	52 (17)	111 (37)	1 (reference category)
100–125	88 (29)	96 (32)	2.3 (1.3–3.8)
125–150	85 (28)	60 (20)	3.0 (1.6–5.7)
>150	76 (25)	34 (11)	(4.8) 2.3–10

Abbreviations: CI, confidence interval; FVIII, factor VIII; OR, odds ratio.
Note: Reprinted from *The Lancet*, Vol. 345, Koster T, Blann AD, Briët E, Vandenbroucke JP, Rosendaal FR, Role of clotting factor VIII in effect of von Willebrand factor on occurrence of deep-vein thrombosis, Pages 152–155. Copyright © 1995, with permission from Elsevier.[6]

Our patients did not show the clinical symptoms of atherosclerosis and we did not find any morphological indicators of this disease (on the basis of ultrasound examination). Although the activating effects of thrombin on different cells participating in the development of atherosclerotic lesions are known, the significance of the coagulation system for the development of the asymptomatic stage of atherosclerosis is unclear. In reports published up until now, no correlation between the level of FVIII and the concentration of thrombomodulin, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (t-PA), intima-media thickness and the level of carotid artery stenosis have been found.[22,23]

Interesting results were obtained in the GAIT (Genetic Analysis of Idiopathic Thrombophilia) study.[24] They indicate a relationship between FVIII and activated protein C (APC) resistance in the pathogenesis of thrombosis. APC resistance increases the risk of the development of venous thrombosis. According to Soria et al, a newly described locus on chromosome 18 modulates FVIII and APC levels in individuals with the absence of factor V Leiden mutation.[25] According to the authors, a high concentration of FVIII is associated with an increase in the susceptibility to thrombosis in different vascular beds.[25] In addition, it seems that abnormal FVIII is responsible for the increase in the number of thrombotic events in patients with neoplastic diseases.

The spread of the neoplastic disease (solid tumors), the location of the disease in the gastrointestinal tract and the young age of the patients turned out to be states more often associated with abnormal concentrations of FVIII. Vascular endothelial growth factor (VEGF) influences the expression of FVIII in endothelial cells. In solid tumors, the participation of VEGF in the process of angiogenesis can explain changes in the concentration of FVIII. Vormittag et al found that an increase in the level of FVIII by 20% causes an increase in the risk of symptomatic venous thrombosis by up to 120%.[14]

The significance of changes in the concentration of FVIII for the occurrence of stroke remains unknown. Its increase was observed in patients with stroke, which caused an interest in FVIII in the aspect of it being a potential risk factor for cerebral ischemic events.[12,13,16] The results of other studies not confirming the relationship between abnormal levels of FVIII and stroke have already been published.[15,26]

The patients we have presented suffered from stroke of an unknown cause. We excluded the presence of traditional or potential risk factors for brain ischemia in all of them. With the use of ultrasound and radiological examinations, focal lesions – including arterial stenosis caused by a thrombus – were visualized in most of them. The cause of the formation of thrombotic material and its origin are difficult to determine in these cases. No characteristic signs of the presence of atherosclerosis were found in the imaging of the walls of arteries. Thrombotic events in the venous or arterial systems had not previously occurred in any of the patients.

Examination for rare causes of stroke revealed increased levels of FVIII when other examined parameters of the coagulation system were normal. In 4 of them, the abnormal concentration of FVIII persisted for the period of 8–10 months after the occurrence of stroke, which suggests that it did not result from additional causes. Finding its incidentally abnormal concentration may result from a secondary activation of the inflammatory process.

This is because FVIII is an acute-phase protein and its concentration increases temporarily during an inflammation. Kamphuisen did not show any correlation between the concentration of FVIII and CRP in patients with venous thrombosis. They also confirmed the persistence of high levels of FVIII several months after a venous thrombotic event.[27] Similar results have been presented by O'Donnell.[28]

The neurological state of our patients in the first 24 hours of the disease indicated serious damage to the functioning of the cerebral hemispheres.

Taking into consideration the clinical features, the course of stroke in the presented patients and the results of additional tests, we concluded that abnormal concentrations of FVIII are a possible cause of stroke. Anticoagulant treatment was carried out to prevent a second stroke.

Over the course of further patient observation (the longest period was 18 months), their neurological state improved and after 3 months from the beginning of the disease, most of them were self-dependent in their everyday social functioning, though neurological signs were present in all of them. In 1 patient, after several months, there was a transient ischemic attack in the other cerebral hemisphere. In the period of the recurrence of the disease, the patient did not use oral anticoagulants.

The coagulation system has an unquestionably basic significance for the occurrence of acute ischemic events. The level of intensity of thrombin generation is associated with an increased incidence of MI and death.[3] The hypothesis that abnormal levels of FVIII are sufficient for the effective activation of the coagulation system and cerebral ischemia remains open. The participation of additional factors, including genetic ones, is probable. In an interesting study, Blann found an increase in the number of venous and arterial thrombotic events in patients who were first-degree relatives with increased FVIII levels.[20]

Taking into account the results of studies published so far and reports regarding small groups of patients with abnormal FVIII levels, one can draw the following conclusions concerning its role in the pathogenesis of thrombosis. The genetic and environmental mechanisms causing abnormal FVIII levels have been only partially understood. An increased concentration of FVIII is a risk factor for thrombosis, especially in the venous system. The probable mechanism of action for elevated FVIII concentration consists in generating thrombin and/or inducing acquired APC resistance in the venous system. It seems that the participation of FVIII in the occurrence of arterial thrombosis consists of activating thrombin and/or increasing platelet aggregation and adhesion in the damaged area of a vessel.

Conclusion

Abnormal concentrations of FVIII are a possible cause of stroke. When searching for the causes of stroke, it is worth considering the examination of the coagulation system, including FVIII concentration, the abnormality of which may play a significant part in brain ischemia. More research is needed to determine the relationship between abnormal FVIII activity and stroke.

Disclosure

The authors report no conflicts of interest in this work.

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