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CASE STUDY

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TAKAYASU ARTERITIS: ASSOCIATIONS WITH HEMOCOAGULATION GENES POLYMORPHYSM

ABSTRACT

Takayasu arteritis (TA) is a systemic vasculitis (SV) subset with chronic granulomatous arteritis predominantly affecting the aorta and its main branches. Cardiovascular events are the leading cause of death in TA patients. The high incidence of cardiovascular events cannot be explained entirely by inflammatory vascular wall lesions. Thrombophilia genes polymorphism has been discussed as another factor of thrombotic events in TA.

The **aim** of the current paper is to demonstrate thrombophilia genes polymorphism identification relevance to better assess the propensity to thrombotic complications in TA patients.

Methods: three clinical cases of verified TA are presented. All had vascular complications. Thrombophilia genes polymorphism, MRI and angiograms assessment were performed.

According to the results of genotyping, the patients were given recommendations on lifestyle modification, further laboratory studies, followed by consultation with the doctor of the rheology laboratory and hemostasis for the selection of personalized therapy with antiplatelet agents or anticoagulants.

The presented cases reflect the undoubted relevance of genetic research. Further research is needed into the specific features of thrombophilic gene polymorphism in patients with Takayasu arteritis.

Keywords: Takayasu's arteritis, thrombophilia genes, polymorphism.

Introduction

Takayasu arteritis (TA) is a systemic vasculitis (SV) subset with chronic granulomatous arteritis primarily affecting the aorta and its main branches [4]. The disease has been reported to occur more often in females [15]. Cardiovascular events are the leading cause of death in TA patients [10]. TA patients have a higher incidence of cardiovascular diseases than in the general population and a significantly higher risk of vascular events on the Score scale at the time of the establishment of the disease in comparison with the general population [6].

Currently, the study of thrombophilia markers is an actual problem. A number of studies have proved the role of polymorphisms of thrombophilia genes and the risk of thrombotic complications in children and young people [3.5], in pregnant women [1, 2].

Clinical case 1

Subject N., a Caucasian female born in 1972. Swelling and pain in the ankle joints occurred in 1998 at the age of 26 a few days after acute cystitis symptoms onset. Small joints of the hands and knee were gradually involved. Non-steroidal anti-inflammatory drugs (NSAIDs) administration had a short-term effect. During 2002-2003 a subfebrile fever was persisting. In April 2005 the subject was regarded as having a chronic course urogenic reactive arthritis. At the same time, a systolic murmur on the right subclavian artery, radial arteries pulse asymmetry,

and humeral arteries 40 mm Hg blood pressure (BP) asymmetry were registered, subfebrile fever persisting. The aorta and its branches ultrasound revealed the visceral branches stenosis, including left renal artery hemodynamically insignificant (<60%) lumen reduction. The above mentioned data being available, no TA has been registered.

The patient has received 3 plasmapheresis procedures accompanied by 3 intravenous 240 mg methylprednisolone infusions and oral sulfasalazine and hydroxychloroquine administration. Though effective, the treatment was discontinued after the discharge. Until February 2012, the subject had been feeling well, unless occasional volatile pains in the small joints of the hands, feet, knees, ankles well controlled by oral NSAIDs.

In February 2012, knees, feet and hands joints polyarthritis occurred, cervical and thoracic spine pain, frequent occipital pain to gradually commence. Dizziness and the evening subfebrile fever up to 37.2 °C also were registered. Total blood count revealed leukocytes = 11.8 x 10^9/L, platelets = 601 x 10^9/L, ESR = 36 mm/H. Serum tests were: hsCRP 3 mg/L, AST 63 IU, ALT 81IU, negative rheumatoid factor (RF), ELISA for chlamydia antibodies was also negative. Chest radiogram was normal. The subject consumed nimesulide on a daily basis.

In 2012 she was hospitalized to the Regional Hospital 1 Rheumatology Dept. BP on the legs was 170/130 mm Hg. In connection with the inflammatory activity (increased ESR, CRP, fibrinogen), it is recommended to prednisone 40 mg / day to normalize the inflammation, then gradually reduce the dose to 7.5 mg / essence. The patient had articular syndrome with involvement of the joints of the hands and feet, periarthritis, pain in the spine. Radiological erosive arthritis of the foot joints was revealed, whose debut was chronologically associated with cystitis, and a urogenital infection was diagnosed several years ago. Patient was recommended radiography of the thoracic spine, the sacroiliac joints. After further examination, taking into account the revealed 2-sided sacroiliitis, grade 1-2, arthritis, enthesitis, urogenital infection, a history of diagnosis was diagnosed.

In November 2013 she was treated in the rheumatology department; pulse therapy was carried out with a metered 250 mg intravenous No. 3. In December 2013, she was transferred to the vascular surgery department, where on December 10, 2013, a brachiocephalic trunk was performed. In the postoperative period (December 11, 2013), an acute disorder of cerebral circulation developed in the basin of the left internal carotid artery. Since that time, I constantly took clopidogrel 75 mg / day. After discharge from the hospital she took prednisone 20 mg / day. Recommendations were followed. She was regularly observed by a rheumatologist.

In March 2015, due to clinical and laboratory activity (ESR = 15 mm / h, ASLO = 165), it was recommended to increase the dose of prednisolone to 15 mg / day. At the same time, she was consulted by an anesthetist. Computer tomography (CT) scan of the brachiocephalic vessels revealed signs of occlusion of both common carotid arteries (OCA) with the development of collateral blood flow in both internal carotid arteries (ICA). Ultrasound of the upper extremities arteries hemodynamically significant disorders of the main arteries were not detected. Surgical treatment is not needed, it is recommended to continue receiving clopidogrel.

Hemostasiogram from 10/17/2016: hematocrit = 30%, platelets = 420 * 109 / l, platelet aggregation with adf = 21%, TTPA = 27.6 seconds, prothrombin time = 14.3 seconds, the Kvik test = 94% , INR = 0.99 , thrombin time = 16.4 seconds, fibrinogen 3.34 g / l, SFC = 5.5 mg / 100 ml, plasminogen activity = 113%. Conclusion: the chronometric parameters of coagulation hemostasis are within the normal range, thrombocytosis is moderately elevated.

Thus, the association of inflammatory lesions of large arteries with the presence of genetically determined thrombophilia led to the development of an acute violation of cerebral circulation. AT and thrombophilia verification allowed us to prescribe anti-inflammatory and antiplatelet therapy and, at least, delay the need for surgical treatment.

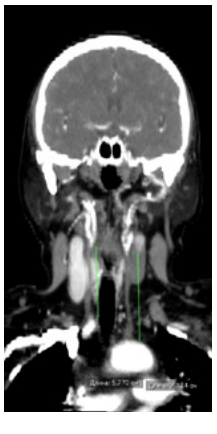

Fig.1. CT Angiography of the head and neck of patient N, coronary projection: long stretches of obliteration of both common carotid arteries

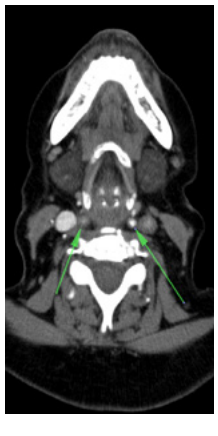

Fig.2. CT Angiography of the head and neck of patient N, axial projection: narrowed gaps of common carotid artery with a pronounced circular thickening of walls

Clinical case № 2

Patient A., female, born in 1963. From her youth, she noted chest pain and shortness of breath during exercise. During the examination in 1994 she noted headaches, severe weakness, accelerated ESR up to 50 mm / h. During the examination, asymmetry of the pulse was noted, the stenosis of the right internal carotid artery (PASA), the right subclavian artery, the left subclavian artery, arterial hypertension up to the maximum figures of 240/130 mm Hg. However AT was not diagnosed.

Since 2002, the patient began to notice intermittent claudication of the lower extremities. Conservative therapy in the form of vascular preparations — Trental 5.0 IV, Cavinton 5.0 IV, and verapamil 80 mg was without effect. On the USDG of the arteries of the lower extremities - stenosis of the iliac arteries, occlusion of the superficial femoral arteries on both sides.

In the spring of 2007, a rheumatologist was examined - taking into account the survey data: noise during auscultation of the carotid arteries, asymmetry of the pulse, young age, stenosis according to instrumental studies, increased ESR in history with exclusion of infection and other causes diagnosed with arteritis Takayasu, started taking prednisone at 30 mg / day In 2007, due to hemodynamically significant stenosis, a bifurcation prosthesis was performed on femoral arteries. Acetylsalicylic acid at a dose of 100 mg / day has been added to therapy. In 2008, a recurrent ultrasound showed signs of stenosis of the internal carotid arteia , subclavian arteries on both sides, stenosis of the common carotid artery on the left, left renal artery . 07/11/2008 endovascular stenting of the common carotid artery was performed. Blood flow in the left common carotid artery was restored. In 2013, she began to re-note pain in the lower extremities, during the examination revealed thrombosis of the right branch of the aorto-femoral (AB) shunt. An operative intervention was performed on June 20, 2013: from the incision in the projection of the femoral access, the right arm of the prosthesis AB, the common femoral artery (OBA), the deep femoral artery. The latter are passable, suitable for reconstruction. In the field of prosthetic and femoral anastomosis were observed occlusion, thrombotic masses. Distal anas-

tomosis of the cross - shunt of the type "end to end" was formed.

Up to this day, she continues to observe rheumatologist, angiologic surgeon SOKB No. 1, continuous intake of prednisone 7.5 mg, aspirin, clopidogrel.

Coagulogram from 2013: hematocrit 39% (35-47), TTPA 41.5 (28-40), the Kvik test 77 (75-120%), INR 1.18 (0.9-1.2), thrombin time 16.4 s (14-21), fibrinogen 3.0 (2-4), SFC 8 mg / 100 ml (0-4.5), plasminogen activity 93% (75-140). Conclusion: increased platelet aggregation, chronometric normal coagulation, increased levels of thrombinemia markers.

In this case, the development of vascular occlusion after reconstructive surgery for hemodynamically significant stenosis was also due to a genetic predisposition to hypercoagulation.

Patient S., female, born in 1959. Ill in 1991: acutely developed fever, weakness. She began to notice pain, paresthesia of the upper limbs. To the doctor did not address. A few months later, an acute violation of cerebral circulation in the PVA pool developed, during the examination there was a decrease in pulsation in the upper limbs, arterial hypertension, systolic murmur over the subclavian arteries. A clinical diagnosis is formulated: AT with lesions of the subclavian arteries, the internal carotid artery on the right. Intake of prednisone was started orally at a dose of 20 mg / day, vascular therapy (Curantil, Cavinton). In satisfactory condition discharged home with the recommendations of observation by a rheumatologist; In view of the complete clinical and laboratory activity, the patient no longer appeared in the Regional Rheumatological Center (RRC). At the telephone contact she complained of shortness of breath, pain retrosternal during physical activity. She was recommended examination by a cardiologist.

In this case, the association of inflammatory lesions of large arteries with the presence of genetically determined thrombophilia caused the development of an acute violation of cerebral circulation at a young age.

We carried out the determination of polymorphisms of hemocoagulation genes in 3 patients with verified AT. All those examined at a young age developed vascular complications in 2 cases in the form of ischemic stroke and in 1 patient thrombosis of the aorto-femoral shunt.

All our patients were carriers of at least 3 allelic variants of thrombophilia genes. It is believed that the risk of recurrent strokes increases in carriers of multigene combinations by 3-7 times [9].

Genetic combinations involving all 3 hemostasis were recorded in all patients: plasma (heterozygous variant of FGB fibrinogen in the first patient, heterozygous variant of the F13 gene in the second patient, and heterozygous variant of the F7 gene in the third patient); platelet (a heterozygous version of the ITGA2 gene is fixed in all patients, a heterozygous version of the ITGB3 gene in the first patient and a homozygous version of the ITGB3 gene in the third); fibrinolysis systems (heterozygous variants of the PAI-I gene in the first and third patients and the homozygous variant of the PAI-I in the second).

Polymorphisms on 7 and 13 clotting factors are considered protective in terms of thrombus formation. Their role as thrombophilic polymorphisms is still under discussion.

It is interesting that ITGA2 and PAI-I polymorphism were noted in all patients. Option ITGA2: 807 (C to T) leads to an increase in the density of collagen receptors on the platelet membrane [7], which, if there is a defect in the endothelial lining, leads to an increased adhesion of platelets and the development of thrombosis in situ.

The PAI-1: 675 variant (5 G to 4 G) acts as an inhibitor of fibrinolysis [14]. Currently, the role of this polymorphism in the development of the immunopathological process is being studied. There is evidence that with the participation of PAI-1, activation of the pre- forms of the

Table 1

Subject N. thrombophilia genes polymorphism assessment (2018)

Factor	Identified subject's genotype	Wild type
F2: 20210 (G на A)	GG	GG
F5: 1691 (G на A)	GG	GG
F7: 10976 (G на A)	GG	GG
F13: (G на T)	GG	GG
FGB: 455 (G на A)	GA	GG
ITGA2: 807 (C на T)	CT	CC
ITGB3: 1565 (T на C)	TC	TT
PAI-1: 675 (5 G на 4 G)	5G4G	5G5G

Table 2

Genetic testing for the determination of genetic markers of thrombophilia from patient A in 2018

Factor	Patients genotype	Wild type
F2: 20210 (G на A)	GG	GG
F5: 1691 (G на A)	GG	GG
F7: 10976 (G на A)	GG	GG
F13: (G на T)	GT	GG
FGB: 455 (G на A)	GG	GG
ITGA2: 807 (C на T)	CT	CC
ITGB3: 1565 (T на C)	TT	TT
PAI-1: 675 (5 G на 4 G)	4G4G	5G5G

Table 3

Genetic testing for the determination of genetic markers of thrombophilia from 2018 patient S

Factor	Patients genotype	Wild type
F2: 20210 (G на A)	GG	GG
F5: 1691 (G на A)	GG	GG
F7: 10976 (G на A)	GA	GG
F13: (G на T)	GG	GG
FGB: 455 (G на A)	GG	GG
ITGA2: 807 (C на T)	CT	CC
ITGB3: 1565 (T на C)	CC	TT
PAI-1: 675 (5 G на 4 G)	5G4G	5G5G

enzymes of the matrix metalloproteinase system is possible [10]. The role of PAI-1 as an inhibitor of cell migration and phagocytosis is also discussed, which also contributes to immunopathological processes [11, 13].

Cases of association of AT and mutations of Leiden were described earlier [16]. However, in the cases presented by us this association was not traced.

In recent years, the characteristic of modern medicine has been given using the "4 P" concept: predictive, personalized, preventive, participatory [12].

From the standpoint of the "4 P" concept, timely examination of patients for polymorphism of thrombophilia marker genes is highly relevant, since an adequate assessment of the risk of vascular complications will allow the timely prevention of condemned events. In addition, evidence has been obtained that the platelet glycoprotein ITGB3 (homo or heterozygous) mutation causes the development of resistance to the antiaggregant effect of aspirin [8]. Identification of genetic markers of thrombophilia allows a personalized approach to the appointment of disaggregant therapy to patients at high risk of thromboembolic complications.

The study of patterns of polymorphism of hemocoagulation genes also allows us to concretize the further scope of laboratory research. For example, the first patient, based on the data of genotyping, should monitor the levels of fibrinogen, SFC, prothrombin time, concentration of plasminogen activator inhibitor, platelet count, thromboelastogram, and platelet aggregation tests.

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According to the results of genotyping, the patients were given recommendations on lifestyle modification, further laboratory studies, followed by consultation with the doctor of the rheology laboratory and hemostasis for the selection of personalized therapy with antiplatelet agents or anticoagulants.

The cases presented reflect the undoubted relevance of genetic research. Further research is needed into the specific features of thrombophilic gene polymorphism in patients with Takayasu arteritis.

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