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Some Laboratory or Functional Methods Detecting Coronary Artery Disease in Asymmetric Dimethylarginine (ADMA), Myocardial Perfusion Scintigraphy, or Both as Sifted Test in Detecting Asymptomatic Edothelial Dysfunction in Patients with Systemic Lupus Erythematosus

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Abstract

Introduction: The purpose of this research was to compare the diagnostic values of laboratory variables, to present quantitative evaluations of the diagnostic test with reference to sensitivity, and specificity, the predictive value of the positive and negative test and precision of the test for Asymmetric dimethylarginine (ADMA), assessed with myocardial perfusion scintigraphy (MPS), acute phase reactant, in early diagnosis of untreated Systemic Lupus Erythematosus (SLE). To determine whether ADMA changes depend on the disease evolution. ADMA is used as a indicator for endothelial dysfunction.

Methods: Using the ELISA technology of DLD-Diagnostika-GMBH, ADMA, the serum has been examined in 70 participants (35 SLE who were not treated, 35 controls). In the same time we determined the sensitivity, specificity, predictive value for positive and negative test and accuracy.

Results: Out of 35 examined patients with SLE, in 13 we found the presence of ADMA (sensitivity of the test 37.14%). Myocardial Perfusion Scintigraphy appeared in 17 patients (sensitivity of the test 48.57%). Four patients were ADMA and MPS positive. Among 18 MPS negative patients, 9 patients were ADMA positive. Among 17 MPS positive SLE, the presence of ADMA was found in 4 patients. Among 18 MPS negative SLE, ADMA appeared in 9 patients. In the healthy control group, 8 patients were ADMA positive.

Conclusion: ADMA has low sensitivity, but high specificity from MPS at untreated SLE with coronary artery disease.

Keywords: Asymmetric dimethylarginine (ADMA); Systemic lupus erythematosus, Coronary artery disease

Abbrevations: ADMA: Asymmetric Dimethylarginine; CAD: Coronary Artery Disease; SLE: Systemic Lupus Erythematosus; EBCT: Electron Beam CT; SSAO: Semi-Carbazide Sensitive Amine Oxidase; SDMA: Symmetric Dimethyl Arginine; NOS: Nitric Oxide Synthetase; CRP: C-Reactive Protein; CMR: Cardiac Magnetic Resistance

Introduction

Systemic lupus erythematosus (SLE) is a chronic, autoimmune, inflammatory disorder with multisystem affection. Due to introduction of novel treatment modalities, the long-term survival of patients with SLE has improved, but they are still in risk of increased cardiovascular morbidity and mortality [1-3].

SLE is one of the strongest known risk factor for atherosclerosis, with rapid and progressive evolution, affection of even young patients, mostly asymptomatic for coronary artery disease (CAD). In general, the frequency of CAD in patients with SLE is up to 12% [4] or incidence of CAD is 7-fold higher [5] than in healthy controls, matched for cardiovascular risk factor. The rate of acute myocardial infarction as the primary cause of the death in SLE in different studies has been reported in up to 36% of the patients with SLE or it is 5 times higher than in general population [6]. Young and premenopausal women are at 52

times higher risk for premature and accelerated atherosclerosis and myocardial infarct than the controls matched for age and sex in Framingam study [7].

Several risk factors and mechanism are recognized to anticipate in development of atherosclerotic vascular disease in SLE: traditional CAD-risk factors in complex interactions with SLE-associated factors and treatment, systemic vascular inflammation and endothelial dysfunction of minor coronary arteries and microcirculation as well as a procoagulant tendency associated with anti-phospholipid syndrome. Ischemia due to vasculitis is more frequent in young people with active disease, often of short duration, while/until ischemia caused by atherosclerosis affect more frequently older SLE patients, with longer duration of the disorder and cumulative doses of corticosteroid therapy. Myocardial ischemia in both group of patient remains mainly subclinical/oligo-and asymptomatic/ but with high risk of premature infarct.

Hence, the evaluation of the myocardial perfusion in patient with SLE is of great importance for their risk stratification and management in order to prevent and minimize the high frequency of cardiac events, especially in young to middle-aged SLE patients and premenopausal women. A number of non-invasive diagnostic modalities have been proposed for evaluation of coronary atherosclerosis. Some of them serves as a surrogate marker of vascular disease - electron beam CT (EBCT) for detection and measurement of coronary calcium score [8] and carotid color Doppler ultrasongraphy for detection of carotid plaques [9]. The others- myocardial perfusion scintigraphy with 99mTc MIBI (99mTc SPECT Gated MIBI MPS) [10] and cardiac NMR perfusion study allow assessment of myocardial microcirculation and microvascular coronary dysfunction in the onset of subclinical myocardial ischemia. These noninvasive studies suggest a prevalence of subclinical vascular disease in nearly 35-49% of the patients with SLE [11].

Some patents with SLE, of younger and older-aged group, with atypical chest discomfort, with low to mild risk category for CAD (not extremelly burdened/with moderately burden with traditional and SLE-related risk factors for CAD), but with evidence of the myocardial perfusion abnormalities, detected with 99mTc MIBI SPECT Gated MPS. As noninvasive and sensitive method, myocardial perfusion scintigraphy may be very useful in screening the patient with SLE for coronary and microcirculatory vascular disease.

Biomarkers for Assessment of Endothelial Dysfunction

Few classes of measurable serum proteins are used in the assessment of cardiovascular system:

- Biomarkers of myocyte injury: troponin I, troponin T, creatine kinase isoenzymes (CK-MB), and myoglobin;
- Biomarkers of myocyte stress: natriuretic peptides - A type (ANP), B type (BNP), adrenomedullin, midregional proadrenomedullin, and ST2;
- Biomarkers of remodeling: (MMPs) 1,2,7,8,9; (TIMPs) 1,2; procollagen type III;
- Biomarkers of endothelial dysfunction: P-Selectin, scCAM-1, semi-carbazide sensitive amine oxidase (SSAO), vascular adhesion protein 1 (VAP-1), ADMA and SDMA, von Willebrandt factor, L-arginine, and nitric oxide metabolites (NO⍰);
- Biomarkers of inflammation: CRP, IL-1, IL-6, IL-10, TNF-a
- Neurohormonal biomarkers: endothelin 1 (ET-1), bigendothelin 1 (Big ET-1).

Of the whole markers of the endothelial dysfunction, dimethyl derivatives of the amino acid L-Arginine incite greatest attention. There are two stereoisomer shapes of L-arginine, symmetric and asymmetric derivatives.

Symmetric Dimethyl Arginine (SDMA): This is a methylated derivative of amino acid Arginine. It is eliminated from the body exclusively with renal excretion. Therefore, SDMA plasma concentration is tightly connected with the renal function. Determination of the plasma level of SDMA is important for assessment of renal failure.

Asymmetric Dimethyl Arginine (ADMA): Synonyms (2S-2-amino 5-[(aminodimethylaminomethylen) amino]) pentanoic acid; N, N-Dimethylarginine; at C8H18N4O2 and natural chemical matter are normally present in plasma. They are metabolic products of continual processes of protein modification in cytoplasm in all human cells, tightly connected with essential amino acid L-arginine. ADMA interferes with L-arginine in the production of nitric monoxide (NO) which has key role in the normal endothelial function. NO is synthesized in endothelial cells with the enzyme endothelial nitric oxide synthetase (NOS) (EC 1.14.13.39). It has 3 isoenzyme forms: endothelial (eNOS), neural (nNOS), and in macrophages and in other immune cells (iNOS) involved in immune response. NO is activated through haemoglobin. Physiologic substrate, that is, precursor for NOS in this enzymatic process is L-arginine which is converted into NO and L-citrulline. NOS is inhibited by the endogenous arginine metabolite ADMA. Plasma level of ADMA is increased in SLE.

Materials and Methods

For the purpose of detecting the CAD in asymptomatic patient with SLE, the SLE- related risk factor were estimated (disease activity according to the SLEDAI score system, immunological status, vasculitis marker-CRP, procoagulant factors-antiphopholipid antibodies and endothelial dysfunction marker-endothelin) as well as traditional risk factor for atherogenesis (age, smoking, obesity, diabetes, hypertension, hyperlipidaemia, positive familiar hystory). Myocardial perfusion status was evaluated with 99mTc MIBI SPECT Gated MPS, at rest and

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stress (after i.v. infusion of 0.56mg/kg/4min as pharmacologic stressor), as one-day protocol. Visual and quantitative analysis of perfusion and functional tomoscintigrams were done in order to determine the extensity and intensity of myocardial perfusion abnormalities. Coronary angiography were done in order to differentiate the major coronary artery affection and microvascular endothelial dysfunction.

Statistical Analysis

For testing the significance of differences between two arithmetical means, i.e., proportions the Student-t-test is used to compare the mean parameters of certain numerical parameters between groups, as well as Willcoxon-matched test for independent samples. Sensitivity and predictivity for positive and negative test of the examined markers is determined with the test for sensitivity and specificity. P-value between 0.05 and 0.1 is considered statistically significant. Analysis of the data is performed with the statistical package Statistica 7.0.

Discussion

Atherosclerosis in SLE has unfavorable features - it is premature and accelerated, affecting young and middle-aged patients, especially premenopausal women. Being with subclinical course - asymptomatic or oligosymptomatic for CAD, SLE is associated with high frequency of vascular events and considerable risk for premature death [12,13].

The pathogenesis of premature atherosclerosis in SLE is complex and multi-factorial, and not yet fully understood [14]. The traditional risk factors for atherogenesis (hypertension, obesity, diabetes mellitus, dyslipidaemia, tobacco use, sedentary lifestyle) are more predicitve for atherosclerosis in SLE patients than in age- and sex-matched healthy subjects [15]. However, although relevant, they are not alone responsible for such vascular changes. A number of different SLE – related factors may contribute to the accelerated atherosclerosis: long-length disease duration, high disease- activity score, assessed by SLEDAI score and poor disease- control under the therapy. Anti-SLE therapy per se in a different way may promote or prevent development of atherosclerosis in SLE. Corticosteroids may be indirectly atherogenic increasing the glycaemia and serum concentration of the lipoproteins, or producing or augmenting hypertension in SLE patients. A proatherogenic lipid profile presumed secondary to corticosteroid therapy include: high plasma triglycerides, LDL, VLDL and low HDL. Corticosteroids on the other hand promote anti-inflammatory and immunosuppressive effect, influencing the disease activity and disease related damage. Thus, more aggressive clinical forms of SLE, treated with high cumulative doses of corticosteroid for a long period, may postpone the development of atherosclerosis, instead of less aggressive or undertreated form, with poor control of the disease that appears as a significant risk factor for atherogenesis [9]. Immunos pressive therapy is more likely to be proatherogenic, while treatment with hydroxychloroquinon is protective. Therapy with monoclonal antibodies improve endothelial dysfunction, but are proatherogenic, by lowering the levels of atheroprotective Igm [16].

Atherosclerosis is now recognized as an inflammatory disorder or immune complex mediated systemic inflammatory disease where inflammation has a central place in the atherogenesis. In patient with SLE, high plasma concentrations of C-reactive protein (CRP) appear to be both, a marker and a risk factor of cardiovascular disease independent of other traditional risk factors [17].

As autoimmune disease, SLE produce a wide spectrum of autoantibodies related to atherogenesis – antibodies against oxidized LPL (OLDL), anticardiolipin and HDL and apolipoptrotein as a constitutent of HDL. Concerning the atheroprotective nature of these lipoproteins, the presence of such antibodies may contribute to the accelerated atherosclerosis in SLE and antiphospholipid syndrome [18].

Chronic endothellial dysfunction may be the earliest demonstrable microcirculatory abnormality in the pathogenesis of atherosclerosis in patients with SLE [19,20]. Circulating anti-endothelial cell antibodies as a marker of vascular damage have been demonstrated in correlation with disease activity score. A number of functional methods are proposed for detection od endothelial dysfunction- pulse wave velocity analysis (Johnson), a mesurement of vascular stiffness or in vitro measuring of endothellin-1(ET-1). Plasma concentrations of ET-1 in SLE are significantly higher comparing with control group, especially in patients with active SLE disease.

Because of the wide spectrum of atherosclerotic vascular disease in SLE (atherogenesis, inflammation/ vasculit, endothelial dysfunction and procoagulant tendency) and high frequency of cardiac clinical events which remain underestimated, the screening for the preclinical/subclinical vascular disease in SLE should be in focus of rheumatologists and cardiologists.

Some patients have chest discomfort, atypical for CAD. The period of the disease duration (9 year and 7 year) correlate with the period of the second pick of the bimodal mortality pattern in SLE, due to premature infarct. According to SLEDAI scores, the male patient are in more active phase of the disease, recently becoming negative on ANA, ADNA, antiphospholipid antibodies and lupusanticoagulant. The female patient are immunologically stable for a longer period of the disease. Both patients are on a corticosteroids for more than 1 year, along with resochin. Based on traditional risk factors, both patients are in low to mild risk category for CAD- smoking (male) and dyslipidaemia (both), mild elevation of CRP in female patient. The endothellin value was high in male patient (not measured in female patient). Echocardiography in both patients didn't reveal alterations in global LV function and regional wall motion at basal condition. Myocrdial perfusion scintigraphy with 99mTc SPECT MIBI

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showed more profound myocardial perfusion abnormalities in male patient - 20% of total myocardial mass of the left ventricule with moderate stress-induced ischemia and fixed hypoperfusion segments (SSS=5, SRS=4, SDS=1), followed with segmental hypokinesia at stress. He was referred for coronary angiography which showed no significant coronary artery stenosis. Thus, myocardial perfusion abnormlities detected with 9mTc MIBI SPECT Gated MOS is more likely reflecting the microcirculatory origin- vasculit and or endothelial dysfunction. The female patients were advised to receive antilipemic/statins therapy according to lesser extensity and intensity of the perfusion abnormalities of 10% of myocardial mass of the left ventricle mild stress-induced ischemia.

In some other patients evaluation of myocardial perfusion abnormalities because of older age, much longer duration of SLE and corticosteroid therapy, along with antimalaric therapy, permanently positive antibodies (ANA,ADNA), but negative APL and LAC, persistence of more traditional and SLE-related risk atherogenetic factors (HTA, family history, high values of CRP, as well as endothelin-1) The patient was in moderate risk for CAD and with more extensive and intensive, two vessel's stress-induce myocardial perfusion abnormalities detected with MPS 99mTc MIBI. Along with perfusion abnormalities, MPS detected and moderate stress-induced hypokinesia in the ischemic segments and slightly higher TID parameter. The coronary angiography was performed. Which shows no significant coronary obstruction. Unexpected, but myocardial perfusion abnormalities again resemble microvascular functional affection.

Myocardial perfusion scintigraphy with 99mTc MIBI performed in some patients has detected myocardial perfusion abnormalities of different extensity and intensity, followed with wall motion disturbances. During the last decade several studies has focused on the role of the perfusion scans in detection of atherosclerotic vascular abnormalities in patient with SLE. Myocardal perfusion abnormalities are present in 22-54% of asymptomatic women with SLE, burdened with traditional and SLE-related risk factors for atherogenesis. A number of studies were aimed to investigate the association of abnormal 99mTc MIBI myocardial perfusion scans with a wide spectrum of previously mentioned risk factors. SLE - related risk factors seems to be of greater importance for progressive evolution of atherosclerosis in patients with SLE then traditional CAD risk factors. Clinical pretesting showed that our patients were at low to mild/moderate CAD risk, with low procoagulant tendency, but possible endothelial dysfunction wit higher level of ET-1 in the blood. So, their myocardial microcirculatory abnormalities reflect the earlier phase of SLE atherosclerosis. However, myocardial perfusion abnormalities detected with MPS were shown to be a strong and independent predictor for the hard cardiac events, such as myocardial infarct. These patients should be under the cardiologist's monitoring and regular check-ups. The capability of the method for estimation of the extensity and intensity of myocardial perfusion abnormalities and quantification of LV global and segmental function allow the selection of the patients for angiography in order to elucidate the nature of the perfusion abnormalities- coronary obstruction or microcirculatory endothelial dysfunction. Some authors suggested that asymptomatic women with CAD risk factor should be screened for CAD with 99mTc SPECT MPS, but the first-line test for that purpose are still a metter of debate. Namely, None of the patients with perfusion abnormalities detected with MPS have showed coronary obstruction on angiography. But, the presence of fixed perfusion defects indicate CAD rather than endothelial dysfunction. The subgroup of patients with abnormal MPS and insignificant CAD on angiography, compared with control group are in greater risk of major adverse cardiac events (13% during 24 month follow-up) than controls (4.2%). Some authors suggested that abnormal MPS is a predictor of higher prevalence of coronary and peripheral vascular events than suggest by a normal coronary angiogram.

Coronary microvascular dysfunction could be also identified by stress cardiac magnetic resistance (CMR). Some identified perfusion abnormalities in 44% patients with SLE and chest pain, compared with 0 of 10 healthy control patients, suggesting that SLE should be regarded as a coronary heart disease equivalent, in the same way as diabetes. Some authors, using a noninvasive measuring method showed markedly depressed flow mediated vasodilatation in the brachial artery of patient with SLE. Novel studies focused on the PET estimation of coronary flow reserve in SLE patients without significant CAD or traditional CAD factors showed abnormal values of this marker indicated prolonged vascular inflammation and microvascular dysfunction.

Conclusion

Based upon the clinical and diagnostic findings of presented cases and according to the literature statements, we suggest that the identification of asymptomatic patient with SLE at risk for coronary events remains extremely important and the algorhythm of clinical and diagnostic investigations is needed for risk stratification and management of these patients in prevention of premature myocardial death. Determination of the clinical pretest probability for coronary vascular disorder and assessment of myocardial perfusion abnormalities with non-invasive technique, for example 99mTc SPECT MIBI MPS may help in screening the patient for coronary angiography. Even in the case of microvascular dysfunction, without coronary obstruction, prevention or treatment of CAD traditional risk factors and better SLE disease control under the therapy could prevent or postpone the accelerated development of atherosclerosis and the risk of hard cardiac events.

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