DECREASED GENE TGF-B1 ARE ASSOCIATED WITH RENAL DAMAGE IN FEMALE PATIENTS WITH LYUPUS NEPHRITIS

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ABSTRACT

The pathogenesis, clinic, and treatment of kidney damage in patients with systemic lupus erythematosus (SLE) are considered. It is noted that if at the beginning of the disease signs of kidney damage are present in 25-50% of SLE patients, then later they are detected in almost 60% of adults and 80% of children. Variants of kidney damage in SLE are described.

The pathogenesis of SLE is generally considered on the model of lupus nephritis. The morphological classification of lupus nephritis, features of the main nephrological syndromes, and clinical variants (active and inactive) are presented. It is indicated that the treatment strategy depends on the activity of the disease, the clinical and morphological variant of lupus nephritis.

Keywords: *SLE, lupus nephritis,* TGF-β1, genes.

АННОТАЦИЯ

Рассмотрены патогенез, клиника и лечение поражения почек у больных системной красной волчанкой (СКВ). Отмечено, что если в начале заболевания признаки поражения почек присутствуют у 25-50% больных СКВ, то в дальнейшем они выявляются почти у 60% взрослых и 80% детей. Описаны варианты поражения почек при СКВ.

Патогенез СКВ обычно рассматривают на модели волчаночного нефрита. Приведена морфологическая классификация волчаночного нефрита, особенности основных нефрологических синдромов и клинические варианты (активный и неактивный). Указано, что тактика лечения зависит от активности заболевания, клинико-морфологического варианта волчаночного нефрита.

Ключевые слова: *СКВ, волчаночный нефрит, TGF-β1, гены.*

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease marked by immune-complex mediated lesions in small blood vessels of various organs, especially the kidneys, although other factors may also be implicated in the pathogenesis of the disease. This article focuses on the role of lipids in the progression of glomerular, vascular and tubulo-interstitial lesions in two patients with lupus nephritis associated with pronounced hyper- and dyslipidemia. The pathogenesis of progressive glomerulosclerosis in both patients appears to be multifactorial. In addition to immune complex mediated lupus glomerulonephritis, progressively active in the first patient, severe nephrotic-range persistent proteinuria, arterial hypertension associated with hyperfiltration and hyperperfusion injuries and, to a minor extent, hyper- and dyslipidemia were observed. The heterogeneous manifestations of systemic lupus erythematosus (SLE) are caused by chronic immune dysregulation and pathogenic autoantibody production that leads to progressive end-organ damage. Kidney damage resulting from lupus nephritis (LN) is among the most severe sequelae of SLE, contributing substantially to SLE-related morbidity and mortality.[1] Despite advances in the management of LN, little progress has been made with respect to the adverse outcomes of LN, including chronic kidney disease, end-stage renal disease (ESRD) or mortality. This is particularly problematic in non-Caucasian SLE patients, who are at increased risk of developing LN, with increased disease severity and altered response to treatment protocols.[2] Kidney damage in systemic lupus erythematosus (SLE) remains one of the most common, severe and prognostically important. The possibilities of modern immunosuppressive therapy, on the one hand, have reduced the proportion of patients with end-stage renal failure, and on the other hand, they have demonstrated the prognostic importance of kidney damage for the course of the disease as a whole [1-5]. In a random sample, 25-50% of patients with SLE have signs of kidney damage at the beginning of the disease, and later they are diagnosed in almost 60% of adults and 80% of children [1, 5]. Kidney damage in SLE is currently multi-faceted.

DISCUSSION AND RESULTS

Early detection and treatment of LN are imperative to minimize the risk of inflammation-induced irreversible kidney damage and to preserve renal function. In addition, analysis of pathway-specific immune dysregulation may one day enable personalized, precision medicine for LN. The success of such approaches will require

methods for identifying individuals at greatest risk of developing LN and for defining measures of pathway-specific immune dysregulation to select the most appropriate LN patients for a given pathway-specific biologic treatment. With the advent of lower-cost genome analysis techniques, both of these goals may be met in part by determining each SLE patient's individual genetic risk factors for LN. Genetic association studies have identified over fifty SLE disease susceptibility loci.[3] Loci associated with LN may influence intra-renal mechanisms of LN that directly produce kidney damage as well as extra-renal mechanisms that promote LN through dysregulation of innate, adaptive, and effector mechanisms of inflammation[1] This work reviews genes implicated in the pathogenic mechanisms of LN according to cell types and molecular pathways associated with immune dysregulation (extrarenal etiology) and kidney damage (intrarenal etiology)

Transforming growth factor β1 (TGF-β1) has a large role in the control of autoimmunity. TGF-β1 production by lymphocytes is reduced in systemic lupus erythematosus (SLE). Decreased levels of TGF-β1 might associate to disease susceptibility, activity and organ damage in SLE. However, the correlation between TGF-β1 levels and severity of renal damage in SLE has not been examined.

The present study was undertaken to assess the serum levels of total and active TGF-β1 in 70 female patients with SLE and 21 healthy women. Simple and multiple regression analyses between TGF-β1 levels and the diseases-related variables were performed in patients with SLE.

Serum levels of both total and active TGF-β1 were significantly reduced in patients with SLE compared with levels in healthy controls ($p < 0.01$). Total TGF-β1 levels correlated positively with white blood cell, platelet counts, calculated glomerular filtration rate (GFR), and active TGF-β1 level, and inversely with erythrocyte sedimentation rate (ESR). In multiple regression analysis, ESR and platelet counts remained determinants of total TGF-β1. Total TGF-β1 levels were lower in patients with high disease activity (SLEDAI > 10) and severe organ damage (SLICC > 3). Significantly lower levels of total TGF-β1 were found in patients with severe renal damage, i.e. lower TGF-β1 in patients with 24-h urine protein over 3.5 g than in those with below 3.5 g ($p < 0.05$); lower TGF-β1 in patients with GFR less than 50 ml/min than in those with over 50 ml/min ($p < 0.05$). In contrast, active TGF-β1 only correlated with platelet counts. There was no association between renal damage and the levels of active TGF-β1.

CONCLUSION

This study demonstrates significantly reduced serum levels of both total and active TGF-β1 in women with SLE compared with healthy women. Total TGF-β1 levels are correlated negatively with ESR and positively with blood platelets. Total TGF-β1 levels were lower in SLE patients with high disease activity and severe organ damage. Importantly, the severity of the renal damage was associated with decreased serum levels of total TGF-β1, suggesting that TGF-β1 might be involved in pathogenesis of renal damage caused by lupus nephritis.

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