

Abstract

Depression in patients with Lupus: the role of genetic variability of monoaminergic system

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Introduction

Systemic lupus erythematosus (SLE) is an inflammatory, chronic, multisystemic disease with a complex symptomatology that may involve different organs, including the Central Nervous System (CNS). Depression is one of the most common neuropsychiatric symptoms in SLE. Although aetiology of is far from being identified, it is known to be an expression of biological, psychological and socio-cultural factors. Neurotransmitters, with implications in the development of depression, such as serotonin, dopamine and norepinephrine, have been intensively studied. The decrease of these amines in depressed patients may result from changes in the synthesis, transport, metabolism and action of these neurotransmitters. Several studies have identified some SNPs (Single Nucleotide Polymorphism), in genes that are involved in monoaminergic signalling, that increase the risk for depression.

Apolipoprotein E is a glycoprotein with a major role in transport and metabolism of lipids. It plays an important function in CNS, particularly in development, regeneration and neuronal protection processes. The apoE gene has three common alleles ($\epsilon 2$, $\epsilon 3$ e $\epsilon 4$) characterized by three different protein isoforms. Several studies have shown the relation between $\epsilon 4$ allele and some brain diseases, including Alzheimer's disease.

Aim

The main goal of this study was to evaluate the role of genetic variability of the monoaminergic system in depression and in CNS involvement in SLE patients. We studied 5 SNPs of genes in the serotonin system in particular, HTR1A, HTR2A, TPH1 and TPH2, and one SNP of the COMT gene (dopaminergic system). In parallel, we also studied the polymorphisms of ApoE in the patient's cohort.

Patients and Methods

This study included 187 healthy subjects and 355 SLE patients from the North and the South of Portugal. Sixty seven SLE patients recruited from the Clinical Immunology Unit outpatient clinic in Hospital Santo António, were referred for neuropsychological evaluation in the Neurology Department. Hospital Anxiety and Depression Scale (HADS) was used as a screening for anxiety and depression and Mini-Mental State Examination (MMSE) was used to assess basic cognitive skills. Once characterized, this cohort of patients was divided into groups: SLE patients with depression ($HADS \geq 8$, $n=30$) and without depression ($HADS < 8$, $n=37$), and Neurolupus ($n=30$) and non Neurolupus patients ($n=37$). Patients were diagnosed with Neurolupus, according to the ACR criteria and based on the clinician's experience.

Genotyping of polymorphisms in monoaminergic system genes was performed by Mass Spectrometry (MassARRAY iPLEX – Sequenom), for the total SLE patients and controls. ApoE genotyping was assessed by PCR-RFLP only for SLE patients with neuropsychological evaluation.

Results

None of the studied polymorphisms showed statistical significance when comparing the allelic and genotype frequencies between SLE patients with and without depression and Neurolupus and non Neurolupus. The G allele frequency of rs1386494 polymorphism (TPH2) was higher in SLE patients with depression (0.85 vs 0.72, $p=0.051$). For the HTR1A gene, increased frequency of the G allele in depression cases (0.50 vs 0.42, $p=0.349$), confirms previous observations reported by other groups.

When the analysis of allele frequencies is extended to all SLE patients, an association was observed between the polymorphism rs6311, located in HTR2A gene, and LES. The frequency of the A allele is significantly higher in this cohort of patients when compared with the control population (50% vs 41%, $p=0.012$, OR=1.38, 1.07-1.78).

The frequency of the apoE ϵ 4 allele was similar in SLE patients with and without depression and Neurolupus and non neurolupus (13.0% vs 12.1%).

Conclusion

Among the studied polymorphisms, none was associated with increased susceptibility for developing depression or even Neurolupus. These results do not support an association between ApoE polymorphism and Neurolupus in this cohort of patients, as previously reported. It is necessary to increase the sample size in order to draw conclusions.

This is the first study that reports an association between the serotonin receptor 2A (HTR2A) gene and the development of SLE. After this study, one question arises: "Is there any linkage between depression mechanisms and the mechanism associated with development of SLE?" Although it remains an open question, the evident recognition of serotonin as immunomodulatory amine, may be a starting point for future research in this area.