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**SYSTEMIC LUPUS ERYTHEMATOSUS AS A FIRST PRESENTATION OF
COMMON VARIABLE IMMUNODEFICIENCY ASSOCIATED TO
UNFREQUENT MANNOSE-BINDING LECTIN GENE POLYMORPHISMS**

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Abstract

The association of common variable immunodeficiency (CVID) and Systemic Lupus Erythematosus (SLE) is infrequent. Mannose-binding lectin (MBL) has been shown to play a role in CVID and SLE. The purpose of this study is to describe two cases of CVID who presented as SLE and also evaluate the presence of MBL polymorphisms and MBL serum levels in those patients.

In both patients, SLE was the first manifestation of CVID. In these patients the SLE immunological markers and disease activity disappeared after the development of CVID. They carried the very infrequent MBL haplotype 4Q-57Glu. One of them had a homozygous genotype, whereas the other patient was heterozygous and also presented the haplotype 4P-57Glu that had never been previously detected. Interestingly, this last patient was presenting frequent respiratory tract infections, developed bronchiectasis and had low levels of circulating MBL.

These results may support the role of MBL in the development of autoimmunity in CVID. Further genetic studies are needed to clarify the role of the MBL polymorphisms in the development of autoimmunity in CVID.

Keywords: Mannose-Binding Lectin, Common Variable Immunodeficiency, Systemic Lupus Erythematosus.

Introduction

CVID is a heterogeneous syndrome characterized by failure of B cell differentiation associated to a defective immunoglobulin (Ig) production.

In addition to recurrent bacterial infections, up to 25% of patients with CVID can develop an autoimmune event [1], that in some instance, can be the initial presenting symptom of the disease. Association of CVID and SLE is uncommon, but approximately 1% of the patients with CVID will develop symptoms or laboratory abnormalities than can support the diagnosis of SLE or SLE-like syndrome [1-3].

The underlying aetiology of increased autoimmunity and development of SLE in CVID is not completely understood. Genetic as well as persistent antigen exposure and ineffective antigen clearance in a background of lack of immunologic regulatory mechanisms seem all likely to contribute.

In recent years CVID has been significantly linked in a minority of patients to defects in genes encoding for molecules as ICOS (inducible co-stimulator) [4], TACI (transmembrane activator and calcium-modulator and cytophillin ligand interactor) [5], CD19 (B-lymphocyte antigen CD19) and BAFF-R (tumor necrosis factor superfamily member 13C) [6, 7], but in none of these patients SLE was observed [8]. In addition, a specific MBL allele, a component of the innate immune response, has been strongly associated with overall autoimmune disease in patients with CVID by contributing to both susceptibility to infections and increased frequency of autoimmune and inflammatory manifestations [9].

We describe 2 patients who developed SLE as an initial presentation of probable CVID.

Methods

Case presentations

Case 1

A 15 year-old girl was diagnosed of SLE in June 1994. She presented with malar rash, photosensitivity, polyarthritis, positive antinuclear antibodies (ANA) 1:1280 and raised anti-dsDNA antibodies (200 IU/mL; normal range < 40) for which she was started on oral steroids. Six months later, she was admitted to our hospital with a 2-week history of low grade temperature followed by gait disturbances and acute urinary retention. Physical examination on admission revealed horizontal and vertical nistagmus and left sided hemiparesis. The immunological profile showed positive ANA 1:1280 and anti-dsDNA antibodies (360 IU/mL; normal range < 40 IU/mL), reduced serum C3 level of 75 mg/dL (80-170 mg/dL) and normal immunoglobulin levels. CSF analysis showed PMN pleocytosis (WBC 370 with 89% PMN) and elevated protein content (1.55 g/l; normal range <0.5). Bacterial, fungal and mycobacterium cultures in both blood and CSF fluid were negative; brain and whole spine MRI showed high signal intensity regions on T2-weighted throughout the spinal cord suggestive of encephalomyelitis. Clinical improvement was achieved after pulses of methylprednisolone (1gx3day) followed by intravenous cyclophosphamide (1000 mg) and oral steroids. One week after discharge, the patient presented with a tonic-clonic seizure and was re-admitted with a status epilepticus. Phenytoin infusion was started and the patient had to be transferred to intensive

care for ventilatory support. On discharged she was on prednisolone (50 mg/day), azathioprine (75 mg/day) and carbamazepine (400 mg/day) with good control of her symptoms.

One year later, she developed respiratory symptoms with frequent episodes of productive cough and recurrent chest infections. Laboratory tests showed a new persistent panhypogammaglobulinemia with serum IgG levels of 320 mg/dL (850-1600 mg/dL), IgA levels of 7 mg/dL (75-350 mg/dL), and IgM levels of 20 mg/dL (58-265 mg/dL). ANA and anti-dsDNA antibodies were negative. No specific antibody response was detected after Pneumococcus and tetanus vaccinations. A probable CVID diagnosis was made and intravenous gammaglobulin replacement therapy (0.5mg/kg/month) was initiated. Since then, she continues on replacement therapy and there has been neither clinical nor laboratory evidence of active SLE in the absence of immunosuppressive therapy.

Case 2

In October 2002, a 13-year-old girl was admitted to our hospital with fever, sore throat, mild bilateral cervical lymphadenopathy, polyarthritis, malar rash and a non-specific generalized maculo-papular rash. Laboratory tests revealed a haemoglobin value of 9.8 g/dL. Bacterial and viral screen were negative. The immunological profile showed positive ANA 1:2560, raised anti-dsDNA antibodies (926 IU/mL; normal range < 40 IU/mL) with normal serum immunoglobulin and complement levels. The thoracoabdominal CT showed minimal bilateral pleural effusions. During her admission, the patient developed a progressive jaundice, hepatosplenomegaly and reduced level of

consciousness. Blood test confirmed the diagnosis of an acute hepatitis (ALT 2394 IU/l (< 30 IU/l), AST 848 IU/l (<34 IU/l), alkaline phosphatase 570 IU/l (< 90 IU/l), GGT 469 IU/l (< 40 IU/l), and LDH 11989 IU/l (< 330 IU/l). Hepatitis A, B, C, CMV and EBV viral serologies were negative as well as the liver autoantibodies. There was no history of hepatotoxic drugs. The abdominal ultrasound was normal and the liver biopsy showed changes compatible with autoimmune hepatitis. Treatment with pulses of methylprednisolone (1g x3 day) and oral azathioprine (1.5mg/kg) was started followed by clinical and serological improvement and resolution of her liver dysfunction. One month afterwards, azathioprine had to be stopped due to severe leucopenia (WBC $<1 \times 10^9/l$ (4.9-19.3x10⁹ WBC/l)) that required treatment with granulocyte colony-stimulating factor. Patient was discharge on oral steroids and tacrolimus 1mg/12 hours as maintenance therapy. In 2004, due to persistent polyarthritis, methotrexate (15 mg/week) was introduced in addition to her previous medication. In April 2006, she was re-admitted with a 6-month history of diarrhoea, abdominal pain, malar rash, worsening polyarthritis, and mouth ulcers. Two days prior admission she also developed severe epigastric pain, nausea and vomiting. Raised serum amylase (1403 IU/L (<350 IU/l) and the evidence of pancreatic oedema in the abdominal CT supported the diagnosis of acute pancreatitis. By exclusion, and by the possibility of a drug-induced pancreatitis, tacrolimus and methotrexate were stopped with clinical and biochemical improvement. At that time, several tests were performed including a malabsorption study, oesophagogastroduodenoscopy and colonoscopy that were normal, and a colonic biopsy that only showed non-specific colitis. The most outstanding blood test result was the presence of a new persistent panhypogammaglobulinaemia

with serum IgG levels of 303 mg/dL (850-1600 mg/dL), IgA levels of 17 mg/dL (75-350 mg/dL) and IgM levels of 26 mg/dL (58-265 mg/dL). ANA and anti-dsDNA had become negative. The lack of immune response to pneumococcus and tetanus vaccination supported the diagnosis of probable CVID. Replacement immunoglobulin therapy (0.5 g/Kg/month) was initiated. Until now, she remains on regular replacement therapy and asymptomatic of her SLE in the absence of immunosuppressive therapy.

MBL genotyping and measurement of MBL levels

Ethical approval was obtained by the local Ethical Committee. Genomic DNA was prepared from whole blood using the QIAamp DNA Blood Maxi Kit (QIAGEN GmbH, Hilden, Germany) and 272 bp-polymerase chain reaction (PCR) fragments were generated. Combinations of forward and reverse allele-specific primers (Table 1) were used to amplify fragments which contained the 5'-untranslated region +4 c/t (P/Q) polymorphisms and the exon 1 polymorphisms at codon 57 t/c (57Gly→Glu) as previously described [9]. MBL levels were determined by ELISA (MBL Oligomer ELISA kit, BioPorto Diagnostics, Gentofte, Denmark). Case 1 had the heterozygous genotype 4P-57Glu/4Q-57Glu and case 2 had the homozygous genotype 4Q-57Glu (Figure 1). Serum MBL concentrations were 4,328 ng/mL and 58.4 ng/mL, respectively.

Discussion

Although CVID is a rare disease, the estimated prevalence in the western population is approximately of 1 in 25,000 according to the different studies. Despite respiratory infections being the most common clinical manifestations of

CVID, an increased frequency of autoimmune disorders, granulomatous inflammation and malignancy have been described [2, 10, 11]. Association of CVID and SLE is uncommon. So far, including our two, a total of twenty patients with SLE and CVID have been described in the literature. In the majority of cases, the development of SLE preceded the development of CVID. At the time of the initial diagnosis, patients had normal sera immunoglobulins and it was later that hypogammaglobulinemia developed. While in the majority, the disease activity and immunological markers decreased after the development of CVID, in other patients the disease remained unchanged [3].

Diagnosis of CVID may be masked in those patients presenting with SLE that receive immunosuppressive therapy. Cyclophosphamide, azathioprine, mycophenolate mofetil, rituximab, corticosteroids and other drugs including phenytoin have been reported to cause hypogammaglobulinemia [3, 10-12]. Unlike CVID, drug-induced hypogammaglobulinaemia is reversible and resolves after drug withdrawal. Although our patients received several immunosuppressive agents and antiepileptic treatment during the course of their disease, it seems unlikely that they were the cause of hypogammaglobulinaemia since some agents were only administered during a short period of time and in both patients hypogammaglobulinaemia was severe and sustained despite being stopped.

Different mechanisms may account for the development of autoimmunity in those patients. The first one would be a possible breakdown in central and peripheral mechanisms of tolerance induction or maintenance. The second contributing mechanism would be related to the existing variable degree of immune dysregulation. Thirdly, the innate and adaptive immunity deficiencies

would lead to persistent/recurrent infections and to a defective processing and clearing of external antigens that may result in a chronic inflammation and recurrent tissue damage secondary to end-organ deposition of immune complexes, formation of anti-tissue antibodies, and cross-reactivity between normal tissues and foreign antigens. Finally, there is a genetic predisposition that can also lead to autoimmunity [13].

MBL is a protein belonging to the collectins family that is involved in several of the above mentioned mechanisms and altered levels of MBL seem to play a role contributing to both the development of CVID and autoimmunity [12]. MBL enhances opsonisation of different mannose-rich microorganisms and it takes part in complement activation pathway that is an important component of the innate immunity, the others important functions of MBL are recognition of altered self structures, and modulation of the inflammation [14]. MBL has shown to bind and clear-out DNA molecules [15], its deficiency appears to mildly increase susceptibility to SLE and associations between SLE and different MBL polymorphisms have been also reported [16].

MBL also plays an important role in CVID. Low MBL levels have been significantly associated with an increased frequency of respiratory tract infections and brochiectasis [17]. Recently, low-producing coding alleles and promoter haplotypes for MBL have been correlated to an early age of CVID onset and variations in the +4Q allele have been associated with increased autoimmunity incidence [9]. The exact mechanism by which MBL polymorphisms may play a role in the development of autoimmunity in patients with CVID is not fully understood, but similarly to what occurs in SLE, it is possible that low MBL levels associated with these variants result in defective

pathogen clearance and immune complex formation that ultimately triggering the autoimmune response [18].

In agreement with Mulligan *et al.*, we also found that our two patients with concomitant CVID and SLE carried this allele. Although polymorphisms in the promoter and the coding region of the MBL gene are closely correlated with serum levels of MBL, the functional effects of the +4Q allele are poorly understood. Mullighan *et al.* [9] also found that the MBL 4Q-57Gly haplotype was associated with autoimmune disease in CVID. However, none of our two patients showed this allele combination. Interestingly, case 2, who also had low levels of circulating MBL, presented the haplotype 4P-57Glu. To our knowledge, only a few of the theoretically possible MBL haplotypes have been described [19] and the 4P-57Glu haplotype has never been detected. It is unclear whether the low MBL levels may really be due to this particular haplotype. Even though, we did not perform an analysis of the frequency of this haplotype in the Spanish population, Lozano *et al* [20] could not find it among the 104 Spanish blood donors controls. It is also worth mentioning that, although our patients had the 4Q-57Glu haplotype, the frequency of this allele combination in the general Spanish population is the lowest (1.92 %) among all the other haplotypes [20]. Thus, the MBL haplotypes we have found in our patients may support the role of the innate immune system in the development of SLE and/or CVID. Due to the small sample size, these results should be interpreted with caution.

Conclusion

We have reported two patients with CVID that initially presented with manifestations of SLE. Although the association of both diseases is uncommon,

it should be considered in any SLE patient with persistent hypogammaglobulinemia. Further genetic studies are needed to clarify the role of the MBL gene polymorphisms in the development of autoimmunity in CVID.

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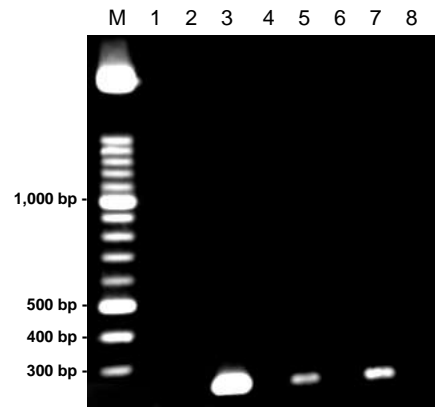


Figure 1.

Figure 1. Mannose binding lectin (MBL) haplotyping for case 1 (lanes 1-4) and case 2 (lanes 5-8). Four double-ARMS PCRs were carried out for each patient in order to detect the four possible haplotypes. The two first reactions (lanes 1-2 and 5-6) were designed to amplify 4P-57Glu and 4P-57Gly haplotypes, respectively. The remaining two reactions (lanes 3-4 and 7-8) were designed to amplify 4Q-57Glu and 4Q-57Gly haplotypes, respectively. PCRs were electrophoresed through a 2% agarose gel. M: 100 bp DNA molecular weight marker.

Table 1.

Primers	Sense/antisense	Sequence (5' to 3')
4P	sense	TAggACAgAgggCATgCTC
4Q	sense	TAggACAgAgggCATgCTT
57GLU	antisense	CCTggTTCCCCCTTTTCTC
57GLY	antisense	CCTggTTCCCCCTTTTCTT

Table 1. Allele specific primers used to amplify the sequence spanning the 5' untranslated region and the codon 57 of MBL exon 1.

