Clinical and Experimental Rheumatology 2010; 28: 558-560.

Hyper IgM syndrome and complement Clq deficiency in an individual with systemic lupus erythematosus-like disease

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Received on February 12, 2010; accepted in revised form on June 25, 2010.

Key words: Hyper IgM syndrome, C1q deficiency, lupus erythematosus-like disease

Competing interests: none declared.

ABSTRACT

Many immunedeficiency syndromes are associated with autoimmune disorders. We here report on a girl with a systemic lupus erythematosus-like disease who suffered from both hyperimmunoglobulin M syndrome (HIGMS) and C1q deficiency. Despite severe central nervous system-lupus like disease, probably due to C1q deficiency, kidney function was relatively spared. IgM autoantibody might play a protective role against lupus-glomerulonephritis.

Introduction

Many immune deficiency syndromes, mainly those involving humoral immunity, are associated with autoimmune disorders. In this report, we describe a girl with systemic lupus erythematosus-like disease, who suffered from both hyper-immunoglobulin M (HIGM) syndrome and C1q deficiency. We speculate that both immunodeficiencies might have contributed to the pathogenesis of systemic lupus erythematosus (SLE)-like disease.

Case report

A 10-year-old Arabian girl presented with a two-day history of cough, high fever, dyspnea and lethargy. Laboratory examination showed an elevated C-reactive protein level (378 mg/L) and leukocytosis (25,600 WBC/mm^3). Chest x-rays demonstrated infiltrations in both the right upper and left lower lobes. Although she responded well to antibiotics, examinations demonstrated low serum levels of both IgG (50 mg/L, ref range; 7900-17400 mg/L) and IgA (20 mg/L, ref range; 630-3730 mg/L), increased serum level of IgM (7520 mg/L, ref range; 100-3800 mg/L) and hypocomplementemia (CH50 0 U/ml, ref range; 28-38 U/ml, C3c 1340 mg/L, ref range; 600-1120 mg/L, C4 340 mg/L, ref range; 140-460 mg/L).

Review of her past history indicated recurrent bacterial infections since infancy. She has been suffering from mucocutaneous manifestations and hip joints pains since she was five years old. Although she was diagnosed with SLE, she was not receiving any immunosuppressive medications due to the family's major concerns about recurrent infections. When she was seven years old, she developed severe central nervous system (CNS) involvement. She developed aphasia and loss of consciousness. MRI of her brain showed multiple ischemic lesions involving both white matter and gray matter of hemisphere with left-sided predominance and also basal ganglia. There was no evidence of occlusive arterial or venous disease. Autoantibodies observed at that time are summarised in Table I. She was treated with repeated intravenous methylprednisolone pulses and intravenous cyclophosphamide initially every two weeks, then every month for six months followed by every three months for additional six doses. She responded well to these therapies, but she continued to have significant neurological sequelae including recurrent seizures.

Family history indicated that her maternal grandmother and paternal grandmother were sisters, which suggested that the patient had an autosomal recessive type hyper IgM syndrome (AR-HIGM). Flow cytometric analysis revealed that 17.1% of PMA-stimulated CD3$^+$ T cells express CD40 ligand (CD40L), comparable to normal controls. Although CD19$^+$, 20$^+$ B cells were decreased (1.78%, ref range; 9.1–21%), most of the B cells were positive for CD40. Among the decreased CD19$^+$ B cells, the percentage of IgD$^+$, CD27$^+$ memory B cells was diminished (5.26%, ref range; 6.1–16.9%). There were no detectable mutations on sequence analysis of the known causal genes of AR-HIGM, including activation-induced deaminase (AID), uracil nucleoside glycosylase (UNG) and CD40 (6). The decreased number of B cells, especially CD27$^+$ memory B cells, and the defective IgG and IgA production suggested a defect in B-cell differentiation or survival as a cause of hyper IgM. The precise causal mechanism is presently under investigation in our laboratory, although secondary effects of immunosuppressive treatments cannot be excluded completely.

Initially, we speculated that her history of SLE-like disease was due to HIGM, because HIGM, especially type 1 (CD40L deficiency) and type 2 (AID deficiency) has been considered

Table I. Auto-antibodies observed when CNS-involvement occurred.

Antibody	Result	Ref. range
Anti Nuclear antibody	1:320 (speckled)	<1:40
Anti-dsDNA antibody	111.5 U/ml	0.0–20.0
Anti-RNP antibody	<6.3 U/ml	0.0–10.0
Anti-Sm antibody	4.7 U/ml	0.0–5.0
Anti-SSA antibody	131.1 U/ml	0.0–4.0
Anti-SSB antibody	48.3 U/ml	0.0–4.0
Ant-SCL70 antibody	<3.1 U/ml	0.0–6.0
Anti-Jo1 antibody	<3.1 U/ml	0.0–10.0
Anti-Cardiolipin antibody		
IgA	<2.7 APL/ml	0.0–10.0
IgG	11.4 GPL/ml	0.0–15.0
IgM	5.4 MPL/ml	0.0–7.0
Anti-B2-Glycoprotein antibody		
IgA	13.0 SA U/ml	0.0–30
IgG	14.5 SG U/ml	0.0–10.0
IgM	6.0 SM U/ml	0.0–12.0
Anti-Phosphatidylserine antibody		
IgG	10.4 GPL/ml	0.0–10.0
IgM	<6.3 MPL/ml	0.0–100.0

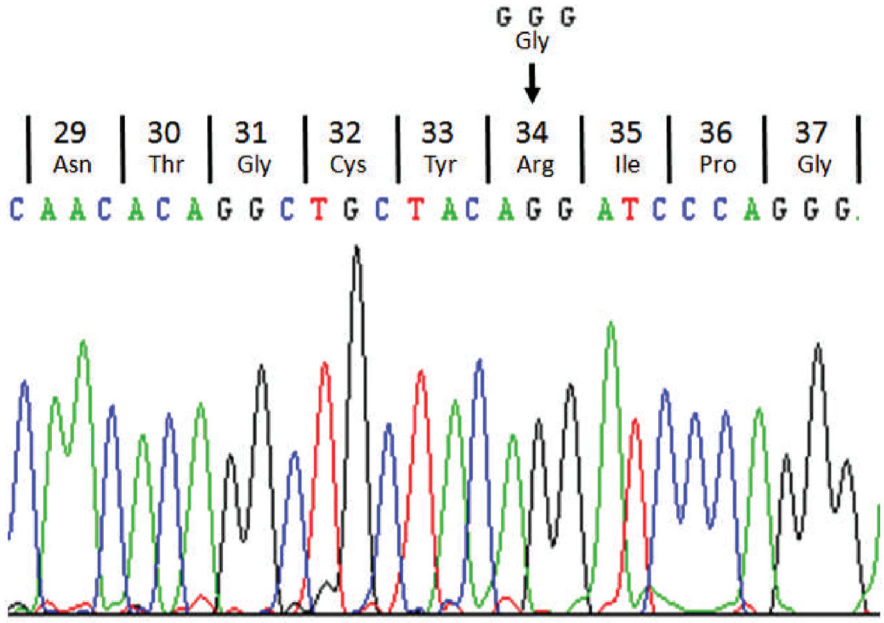

Fig. 1. A homozygous mutation of C1qc gene Gly34Arg. All exons of C1q a, b, and c chain genes were sequenced according to Marquart *et al*. (4).

associated with autoimmune phenomenon (3), and the rare coexistence of HIGM and SLE has been reported (1, 5). However, CH50 activity in this case was persistently low regardless of SLE disease activity. Therefore, we started to investigate her complement system.

Her classical pathway haemolytic activity was 0.034% of the normal control, and serum C1q protein level was 5% of the normal control. When C1q protein, but not C1r nor C1s proteins, was added to her serum, haemolytic activity recovered to 114% of that in normal control serum, suggesting deficiency of C1q protein. Then, we sequenced all exons of C1q a, b, and c chain genes according to Marquart *et al*. (4). A homozygous mutation of C1qc gene Gly34Arg was detected (Fig. 1). This mutation was previously reported in families including those of Saudi Arabian origin (7). The possibility that this patient may have a combined complement deficiency was excluded because her AP50 was 146% of normal control.

Discussion

HIGM syndromes are a heterogeneous group of primary immunodeficiency disorders, characterised by decreased serum levels of IgG, IgA, and IgE and normal to increased serum levels of IgM (6). Although HIGM have previously shown to be caused by mutations in the genes encoding CD40L, CD40, AID, and UNG, the molecular basis of remaining cases of HIGM is still unknown. Of these, at least two distinct forms have been recognised, and impaired targeting of AID onto S regions and yet unidentified DNA repair systems are regarded as a candidate cause of these HIGM. From a clinical point of view, lymphoid hyperplasia is reported milder in the former than the latter (6). As our patients did not develop lymphoproliferative symptoms, impaired targeting of AID onto S regions is more likely as the cause of her HIGM.

The relationship between complete deficiency of any of the early components of the classical complement pathway and the development of SLE has been established (2). SLE or lupus-like manifestations have been identified in 93% of homozygous C1q-deficient individuals. SLE in homozygous C1q-deficient individuals characteristically shows a high frequency of central nervous system disease and C1q-deficiency leads to lupus nephritis in approximately a third of the patients. These observations could be explained by the hypothesis that C1q is essential for proper clearance of apoptotic cells and immune complexes (IC). In our case, urinalysis was persistently normal suggesting that the kidney had been spared, although renal biopsy was not performed. As lupus-nephritis is regarded as a typical IC disease, paucity of IgG autoantibodies caused by class switch defect might play a protective role. Furthermore, glomerulonephritis was reported to be rare in SLE patients with IgM autoantibodies (8). IgM autoantibodies may bind to antigen and block the formation of pathogenic ICs consisting of IgG autoantibody which leads to IC mediated nephritis. In contrast pathological process mediated by functional autoantibodies such as lupus-anticoagulant might not be protected by IgM auto-

antibodies, because both IgM and IgG lupus-anticoagulant have anticoagulant activity.

Acknowledgments

We thank Dr M. Matsumoto from Hokkaido University for generously donating purified C1r and C1s.

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