Case report

Heterozygous C2 deficiency associated with angioedema, myasthenia gravis, and systemic lupus erythematosus

J EFTHIMIOU, D D'CRUZ, P KAPLAN, AND D ISENBERG

From the Department of Medicine, University College London School of Medicine, The Rayne Institute, University Street, London

SUMMARY We describe a patient with myasthenia gravis, systemic lupus erythematosus, and angioedema associated with heterozygous complement factor 2 (C2) deficiency. The significance of this association is controversial, though the association of C2 deficiency with certain histocompatibility antigens suggests possible linkage to immune response genes. To our knowledge this is the first report of heterozygous C2 deficiency in association with this combination of 'autoimmune' disorders, and we discuss the aetiological implications.

The coexistence of myasthenia gravis and systemic lupus erythematosus (SLE) is well recognised,¹⁻⁵ though the association of these two conditions with angioedema has only once previously been reported.⁵ Homozygous and, less commonly, heterozygous deficiency of complement factor 2 (C2) is also recognised in association with SLE⁶⁻⁸ but has not previously been described in association with myasthenia gravis. We report on a patient with angioedema, myasthenia gravis, and SLE who had heterozygous C2 deficiency.

Case history

A 36 year old Caucasian woman known to have myasthenia gravis was admitted to hospital with a one year history of intermittent polyarthritis involving the hands, knees, and ankles, Raynaud's phenomenon, and urticarial rashes associated with swelling of her lips and tongue.

At the age of 16 years she presented with bilateral ptosis, dysarthria, and dysphagia. Myasthenia gravis was confirmed by electromyography, and she responded well to treatment with pyridostigmine.

Examination showed swollen tender metacarpophalangeal and ankle joints, with an urticarial rash over her arms. Auscultation of her chest showed bilateral late inspiratory crepitations over both lung bases.

She had an erythrocyte sedimentation rate (ESR) of 58 mm/1st h (Westergren), antinuclear antibody (ANA) titre of 1/640, with a diffuse (homogeneous) pattern, DNA antibody titre of 38 U/ml (normal <25 U/ml), skeletal muscle antibody, and acetylcholine receptor antibody titre of 4×10^{-10} mol/l (normal $<2 \times 10^{-10}$ mol/l). The C2 level was 45% of normal, the total haemolytic complement (CH₅₀) 50% of normal, and increased levels of circulating IgG and IgM immune complexes (determined by C1q binding) were detected. Histocompatibility antigen (HLA) typing showed that she was HLA-A1 and B8 positive. The full blood count (including white cell count and lymphocyte number), urea, electrolytes, creatinine clearance, and levels of complement factors C3 and C4 and C1 esterase inhibitor were normal.

The chest radiograph showed reticulonodular shadowing over both lower zones. A computed tomographic scan of the thorax disclosed evidence of a thymoma. Transbronchial lung biopsy showed fibrosis and chronic inflammation of the alveolar walls consistent with fibrosing alveolitis.

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Correspondence to Dr J Efthimiou, Department of Medicine, The Rayne Institute, University Street, London WC1E 6JJ.

A diagnosis of SLE, angioedema, myasthenia gravis, and heterozygous C2 deficiency was made. A healthy 11 year old son who was HLA-A1 and B8 positive was also found to have a reduced C2 level (60% of normal) and an ANA titre of 1/80, with a diffuse (homogeneous) pattern. The mother, one sister, and two daughters of our patient all had normal levels of C2. Her father and husband were not available for study.

She was initially treated with naproxen for the polyarthritis and chlorpheniramine and cimetidine for the urticaria and angioedema and made a good response. Three months after cimetidine treatment was stopped she was readmitted with a more extensive urticarial rash involving her arms, abdomen, and neck, with swelling of her lips and tongue. She was treated with subcutaneous adrenaline, intravenous chlorpheniramine, and hydrocortisone, which resulted in prompt clearance of the angioedema. Cimetidine therapy was recommenced and prednisolone (30 mg daily) added, with complete resolution of the polyarthritis.

At follow up one year later while still taking prednisolone (7.5 mg on alternate days) she remained asymptomatic. Investigations at that time showed the ESR was 21 mm/1st h, the ANA titre 1/80, and the C2 level 51% of normal.

Discussion

Homozygous C2 deficiency is the commonest inherited complement factor deficiency.⁹ Homozygous C2 deficiency occurs in approximately one in 10 000 to one in 40 000 of the normal population and heterozygous C2 deficiency (i.e., with C2 levels of approximately 50% of normal) in up to 2% of the population.^{6 10 11} The gene determining C2 deficiency, i.e., C2D, appears to be inherited as an autosomal codominant with a marked predominance in females, who show a significantly higher incidence of rheumatic diseases than males (i.e., 25.7% of affected females compared with 4.2% of affected males).¹² Both homozygous and heterozygous C2 deficiencies are known to occur in association with SLE.^{7-9 13} A large number of diseases have been linked with homozygous C2 deficiency, including anaphylactoid purpura, undiagnosed arthritis, dermatomyositis, chronic vasculitis, Hodgkin's disease, idiopathic membranous glomerulonephritis, and recurrent infections,^{7-9 13} though many individuals (approximately 40%) may have none of these problems and appear perfectly healthy.¹³ Heterozygous C2 deficiency has also been associated with a variety of rheumatic and non-rheumatic disorders, including juvenile rheumatoid arthritis, arthralgia of unknown aetiology,

rheumatoid arthritis, chronic glomerulonephritis, psoriasis, and recurrent infections.^{10 12 14}

SLE is known to occur in association with myasthenia gravis,¹⁻⁵ but there has been only one previous report of these two conditions in association with urticaria.⁵ In addition, SLE and particularly SLE-like syndromes are recognised to occur in association with hereditary angioedema due to C1 esterase inhibitor (C1 EI) deficiency,^{14a-17} as well as with acquired complement deficiency states.^{12 13} Furthermore, patients with hereditary C1 EI deficiency, who may show a marked depression of C2 and C4 levels both during and between attacks of angioedema,^{13 16-18} have been known to develop SLE and discoid lupus erythematosus.^{14a 15} In a twin study of hereditary angioedema one of a pair of female twins showed a marked deficiency of C2 and C4 levels and later developed SLE.¹⁷

Myasthenia gravis has not previously been described in association with depression or deficiency of the early complement components. A genetic susceptibility to myasthenia gravis, however, is suggested by the finding of an association with HLA-A1 and B8.¹⁹ In addition, there is a close positive linkage between the gene determining C2 deficiency and the HLA genes A10, B8, and Dw2,^{12 20 21} and these genes also occur in close association with SLE and SLE-like disorders.¹²

It seems unlikely that the association of C2 deficiency and SLE, two relatively rare conditions, is purely coincidental. Deficiency of early complement components is likely to compromise the host's ability to eliminate antigens and this may give rise to immune complex mediated disease.^{9 13} There is some evidence that persistent infection with a virus may produce lupus-like syndromes, and that deficiency of factors required to form C3 convertase could lead to a reduced ability to eliminate the virus from the serum, thus leading to immune complex formation and disease.^{9 22 23} Another possibility is that the complement deficiency is a marker for a closely linked genetic locus which itself determines the disease.⁹ This argument is supported by the studies of Glass *et al*¹⁰ and could apply to our patient, who has a heterozygous C2 deficiency and is HLA-A1 and B8 positive. Together, these determinants may be markers for a genetic susceptibility to the development of SLE, angioedema, and myasthenia gravis.

We have described a patient with heterozygous C2 deficiency who developed angioedema, myasthenia gravis, and SLE, and was HLA-A1 and B8 positive. To our knowledge this is the first report of C2 deficiency associated with myasthenia gravis, though SLE and angioedema are well known to occur with C2 deficiency. Further similar reports

may throw more light on the relationship of complement factor deficiencies and the development of autoimmune and other immunologically mediated diseases.

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