

Case report

SLE-like and sicca symptoms in late component (C9) complement deficiency

M SUGIMOTO,¹ M NISHIKAI,¹ A SATO,¹ Y SUZUKI,² M NIHEI,²
J UCHIDA,² AND N MIMURA²

From the ¹Department of Internal Medicine and Clinical Study, Second Tokyo National Hospital, Tokyo; and the ²Kidney Center, Toranomon Hospital, Kanagawa, Japan

SUMMARY Hereditary deficiencies in early and late complement components are well known to predispose to SLE-like syndromes or recurrent infection. Hitherto reported C9 deficient cases have usually been healthy subjects, however, and it is not considered that C9 deficiency is associated with any specific disease. We describe a completely C9 deficient patient with possible Sjögren's syndrome and discuss the relationship.

It has been reported that a deficiency of specific complement (C) components, especially C2 and C4, may predispose to systemic lupus erythematosus (SLE), or SLE-like syndromes.¹ C9 deficiency (C9D) was first described by Inai *et al* in 1979.² In this paper we describe a case of complete C9 deficiency with possible Sjögren's syndrome.

Case report

In February 1983 a 48 year old Japanese housewife developed dry eyes, dry mouth, fever, joint pain, and weight loss and two months later was admitted to our hospital. On physical examination she was thin, pale, and febrile (37.6°C). Lymph nodes were swollen in the cervical and inguinal regions bilaterally. The liver was slightly enlarged, but the spleen was not palpable. Neurological examination showed no abnormal findings. Her peripheral joints did not show any objective findings of active synovitis, though she had a past history of arthralgia.

Laboratory tests showed haemoglobin 10.5 g/dl (105 g/l), white blood cells 2800/mm³ (2.8×10⁹/l) platelet count 29.1×10⁹/mm³ (291×10⁹/l), normal liver function, normal renal function, normal serum electrolyte values, and normal urine analysis.

Antinuclear antibodies (ANA) by the indirect immunofluorescence method with rat liver cells as a

substrate and the rheumatoid factor were negative. LE cells and antinative deoxyribose nucleic acid (DNA) antibody by passive haemagglutination and the Crithidia method were negative. Precipitating antibodies to Sm, nuclear RNP, Ro/SSA, and La/SSB were all absent. C3 and C4 values were normal, but despite repeated assays the CH₅₀ value was always low (5–15 U/ml; normal 30–40 U/ml). A chest radiograph showed no remarkable findings. The electrocardiogram was normal. The gum test (stimulated whole salivary flow rate using chewing gum as stimulant) was 11 ml/10 min (normal >10 ml/10 min). The sialogram and biopsy of the labial gland were normal. The rose bengal test, fluorescent test, and Schirmer's test (right 1 mm, left 5 mm) were all positive, indicating the presence of keratoconjunctivitis sicca. Biopsy of the cervical and inguinal lymph nodes showed non-specific lymphadenitis. On admission she had a recurrent oral ulcer, which was improved by the administration of 20 mg of prednisolone daily. Later she occasionally fainted for a few minutes and had transient global amnesia for several hours, but an electroencephalogram, brain computed tomographic scan, and cerebrospinal fluid study showed no remarkable findings.

Since CH₅₀ levels of her sera always showed less than half of the normal level, her other complement components were studied (Table 1). Values of C1INH, C1q, C2, factor B(Bfs), and C5 were all normal, but the C9 component was undetectable.

Table 1 Complement components profile of the patient

	CH ₅₀	CIINH	CI _q	C1	C4	C2	B	C3	C5	C9	C3T
Normal pool serum*											
Haemolytic assay (U/ml)	40 (10)	2253		55 000	120 000	630		91 000	60 000	68 000	2400
Protein assay†			10.0 (26) (%)		22 (13) (mg/dl)		16 (8) (mg/dl)	65 (16) (mg/dl)	100 (30) (%)	100 (%)	
Patient											
Haemolytic assay (U/ml)	15	4224		20 000	77 000	500		31 000	35 000	0	0
Protein assay†			102 (%)		17 (mg/dl)		11.0 (mg/dl)	70 (mg/dl)		ND‡	

*Values are mean (2 SD).

†Protein assay values are given in mg/dl or % normal human serum.

‡ND = not detected.

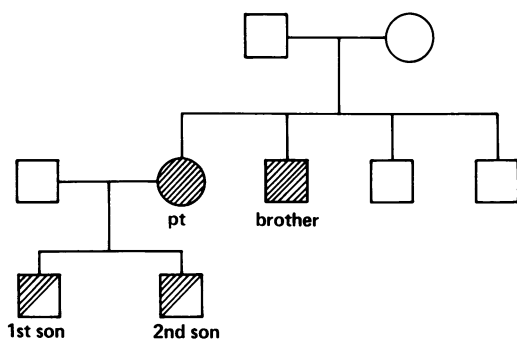


Fig. 1 Pedigree of the C9 deficient family. □=male; ○=female; □, ○= not examined; ▨, ●=homozygote (completely deficient); ▩, ⊙=heterozygote (partially deficient).

The C9 haemolytic level was fully recovered when purified C9 was added to her serum. Accordingly, she was diagnosed as having C9D. In addition, study of her family showed that her brother had complete C9D and that both her sons had partial C9D. (Fig. 1).

Discussion

The significance of complement deficiency (CD) in the pathogenesis of connective tissue diseases is not clearly understood, but the association of CD with connective tissue diseases has been supported by an increased incidence of SLE or related syndromes in patients with CD.

In this patient the clinical features suggest some type of rheumatic disease, but most of the features were not disease specific. The oral ulcer, which responded to prednisolone therapy, and the arthralgia were compatible with SLE, but no serological confirmation was obtained. Dry eyes and ophthalmological examinations indicated the presence of

keratoconjunctivitis sicca. Therefore, a diagnosis of Sjögren's syndrome with complete C9D appeared most likely. Family studies indicated that the deficiency was inherited as an autosomal dominant trait (Fig. 1).

Previously reported Japanese cases of C9D showed it to occur in usually healthy subjects and among them recurrent infections were seen only very rarely.^{2,3} The studies on C9D sera haemolytic and bactericidal activity showed that the rates of cytolysis of erythrocytes and bacteria were slower in the C9 deficient sera, but reached completion eventually.^{4,5} Furthermore, no increased susceptibility to viral disease has been observed in patients with C9D. For these reasons it appears unlikely that such deficiency would, through persistence of an infectious agent, result in a connective tissue disease.

Early component deficiency may impair complement function in solubilisation of immune complexes and decrease their clearance. But it has been reported that late components (C5, C6, C7, C8, and C9) are not involved in this phenomenon.⁶ Accordingly, in a late component deficient state such as C9D, abnormal immune clearance cannot be incriminated in the development of the associated connective tissue disease.

On the other hand, it has been shown that both connective tissue diseases and CD are linked with HLA. For example, the loci which are associated with SLE are DR3 in Caucasians⁷ and DR4 in Japanese.⁸ In addition, it is clear that there is a close linkage between the genetic loci for Bf, C2, and C4 and those for HLA,⁹ and close positive linkage is well established between the C2D gene and HLA genes A10,¹⁰ B18,¹¹ Dw2,¹¹ DR2,¹² and between the C4D gene and HLA genes A2, Bw40, Cw3.¹³ Therefore, it is conceivable that CD is in linkage disequilibrium with a defective immune response gene, leading to connective tissue disease.

These linkages may determine the susceptibility

to connective tissue diseases in complement deficient patients. Although there have been no reports yet suggesting a linkage between C9D and HLA, in deficiency of C8, which has similar functions to C9, two cases with SLE have been reported.^{14 15}

Although the relation between CD and connective tissue diseases is not understood, it is supported by the many cases of SLE or SLE-like syndrome that have been reported in patients with CD, some of them in late component deficiency.¹⁴⁻¹⁸ In the lupus syndrome seen in complement deficient patients the less positive serology, including ANA and antinative DNA antibodies, is one of the characteristics.¹ So we must follow up this patient carefully to see whether she develops definite SLE or Sjögren's syndrome, or both in the future. Until now it has been believed that nothing connects C9D with any connective tissue disease and that its clinical significance is extremely limited. The existence of this case of a systemic rheumatic syndrome with C9D, however, suggests a relation with connective tissue disease similar to that of other CD.

References

- 1 Agnello V. Complement deficiency states. *Medicine (Baltimore)* 1978; **57**: 1-23.
- 2 Inai S, Kitamura H, Hiramatsu S, Nagaki K. Deficiency of the ninth component of complement in man. *J Clin Lab Immunol* 1979; **2**: 85-7.
- 3 Kitamura H, Nagaki K, Inai S. Further studies on C9 deficiency. *J Clin Lab Immunol* 1981; **6**: 7-11.
- 4 Lint T F, Zeite H J, Gewurz H. Inherited deficiency of the ninth component of complement in man. *J Immunol* 1980; **125**: 2252-7.
- 5 Harriman G R, Esser A F, Podack E R, et al. The role of C9 in complement-mediated killing of *Neisseria*. *J Immunol* 1981; **127**: 2386-90.
- 6 Takahashi M, Czop C, Ferreira A, Nussenzweig V. Mechanism of solubilization of immune aggregates by complement. Implications for immunopathology. *Transplant Rev* 1976; **32**: 121-39.
- 7 Black C M, Welsh K I, Fielder A, Hughes G R V, Batchelor J R. HLA antigens and Bf allotypes in SLE. *Tissue Antigens* 1982; **19**: 115-20.
- 8 Kamada S, Naito S, Tanaka K, et al. HLA antigens of patients with systemic lupus erythematosus in Japan. *Tissue Antigens* 1982; **20**: 221-2.
- 9 Alper C A. Complement and the MHC. In: Dorf M E, ed. *The role of the major histocompatibility complex in immunology*. New York and London: Garland STPM Press, 1981: 173-220.
- 10 Fu S M, Kunkel H G, Brusman H P, Allen F H Jr, Fotion M. Evidence for linkage between HL-A histocompatibility genes and those involved in the synthesis of the second component of complement. *J Exp Med* 1974; **140**: 1108-11.
- 11 Schur P H. Genetics of complement deficiencies associated with lupus-like syndrome. *Arthritis Rheum* 1978; **21** (suppl): 153-60.
- 12 McCarty D J, Tan E M, Zvaifler N J, Koethe S, Dugesnoy R J. Serologic studies in a family with heterozygous C2 deficiency. *Am J Med* 1981; **71**: 945-8.
- 13 Richter C H, Hauptmann G, Grosse-Wilde H, Tongio M M, Mayr S. Linkage between HL-A (major histocompatibility complex) and genes controlling the synthesis of the fourth component of complement. In: Kissmeyer-Nielsen F, ed. *Histocompatibility testing*. Copenhagen: Villadsen and Christensen, 1975: 945-53.
- 14 Jasin H E. Absence of the eighth component of complement in association with systemic lupus erythematosus-like disease. *J Clin Invest* 1977; **60**: 709-15.
- 15 Pickering R J, Rynes R I, Locascio N, Monahan J B, Sodetz J M. Identification of the alpha-gamma subunit of the eighth component of complement (C8) in a patient with systemic lupus erythematosus and absent C8 activity: patients and family studies. *Clin Immunol Immunopathol* 1982; **23**: 323-34.
- 16 Rosenfeld S I, Kelly M E, Leiby J P. Hereditary deficiency of the fifth component in man. *J Clin Invest* 1976; **57**: 1626-43.
- 17 Trapp R G, Mooney E, Hussain I, Coleman T H, Forrestal J, Herman J H. Hereditary complement (C6) deficiency with discoid lupus/Sjögren's syndrome. *Proceedings of the Annual Meeting of the Heberden Society, London* 1980.
- 18 Zeitz H J, Miller G W, Lint T F, Ali M A, Gewurz H. Deficiency of C7 with systemic lupus erythematosus. Solubilization of immune complexes in complement deficient sera. *Arthritis Rheum* 1981; **24**: 87-93.