Mesangiocapillary Glomerulonephritis Associated with Hereditary Angioedema

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Dear Sir,

Hereditary angioedema (HAE) due to deficiency of C_1 inhibitor is a rare autosomal dominant transmitted disorder, manifested by recurrent attacks of nonpitting edema, generally involving extremities, face, and upper airways [1]. Deficiency of C_1 inhibitor results in the unopposed enzymatic activity of C_1 , leading to cleavage of C_2 and C_4 and, consequently, low serum levels of these proteins [1]. We report a case of a patient with HAE who developed mesangiocapillary glomerulonephritis (MCGN) under observation. The coexistence of these two rare disorders suggests that they may be linked to each other and adds further support for the contention that prolonged hypocomplementemia predisposes to the development of glomerulonephritis [2]. This 20-year-old man was referred to our hospital in December 1992 because of edema of the lower extremities, proteinuria, and hematuria. There was a family history of HAE (father and brother), and at the age of 14 years a diagnosis of HAE was established in the patient. He had suffered from recurrent attacks of swelling of the extremities and the face, sometimes accompanied by dyspnea, difficulties with swallowing, and abdominal cramps, requiring hospitalization on several occasions. He denied dysuria, fever, arthralgias, skin rashes, or photophobia. He used danazol 200 mg once daily. Physical examination on admission revealed discrete ankle edema. The blood pressure was 120/85 mm Hg. Urinalysis showed numerous red blood cells (140-300/ml) and protein 3+. The urinary protein excretion was 5.2 g/24 h. Other relevant laboratory data included serum creatinine 85 (normal 60-110) $\mu\text{mol/l}$, urea 5.6 (normal 2.5-8.0) mmol/l, protein 62 (normal 65-80) g/l, and albumin 35 (normal 36-48) g/l. Antinuclear antibody and anti-DNA titer were negative. Complement studies revealed low levels of C_1 inhibitor activity (< 0.05 , normal 0.76-1.33 μml) and C_4 (80, normal 140-343 mg/l). The C_3 level was 1.11 g/l, C_3 -nephritic factor was not detectable. Circulating immune complexes (C_1q binding 20, normal $< 7\%$) were present. Renal biopsy showed mesangial hypercellularity and increased mesangial matrix with compression of the capillary loops. The glomerular basement membrane was thickened, and focally a 'double contour' was seen due to mesangial interposition. Immunofluorescence showed peripheral distribution of IgG, IgM, IgA, and C_1q . The findings were compatible with the diagnosis of MCGN type I.

HAE has been reported as one of several complement-deficient states associated with autoimmune diseases, most notably systemic lupus erythematosus (including lupus nephritis) [1,3]. To date, 6 patients have been reported with HAE who developed glomerulonephritis without clinical or serological evidence of systemic disease [4-8]. As in the present case, 5 of these patients had type I MCGN, whereas 1 patient had diffuse proliferative glomerulonephritis. All patients exhibited low levels of C4. Two of these patients also exhibited low serum levels of C3, however, the presence or absence of C3-nephritic factor was not mentioned in these cases. Two possibilities regarding the pathogenic role of the complement system in the development of MCGN in these patients exists. In type II and, to a lesser extent, type I MCGN, the C3-nephritic factor may be present which leads to persistent complement activation by the C3b feedback cycle [4, 5].

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By analogy, persistent complement activation because of lack of an inhibitor may be the major damaging process in HAE, thereby directly leading to glomerular injury [4,5]. Secondly, resulting chronic hypocomplementemia may predispose to the development of renal disease. Chronic hypocomplementemia occurs in many cases of MCGN. Patients with type I MCGN may have low serum levels of C1q, C4, or C5, whereas in patients with type II MCGN low serum levels of C3 are often observed, sometimes associated with the presence of C3-nephritic factor [9]. In addition, the development of MCGN in patients with an inherited deficiency of components of the complement system, usually C2 or C3, has been described on several occasions [2,4].

Combined data suggest that chronic hypocomplementemia, either as the consequence of persistent activation of the complement system or as a result of an inherited deficiency, may precede and predispose to the development of MCGN. As MCGN may be an immune-complex-mediated disease, defective clearance of circulating immune complexes as a result of complement deficiency may be involved [10].

References

Sim TC, Grant JA: Hereditary angioedema: Its diagnostic and management perspectives. *Am J Med* 1990;88:656-663.

Coleman TH, Farristal J, Osaka T, West CD: Inherited complement component deficiencies in membranoproliferative glomerulonephritis. *Kidney Int* 1983;24:681-690.

Young DM, Thompsons RA, Made PH. Plasma-pheresis in hereditary angioneurotic edema and systemic erythematosus. *Arch Intern Med* 1980; 140:127-128.

Pickering RJ, Michael AF, Herdman RC, Good RA, Gewurz H: The complement system in chronic glomerulonephritis. Three newly associated aberrations. *J Pediatr* 1971;78:30-43.

Plaza J, Malasit P, Kerr DNS: Hereditary angioedema with mesangiocapillary glomerulonephritis. *Postgrad Med J* 1977;53:627-630.

Spitzer RE, Stitzel AE, Urmson JR: Hereditary angioneurotic edema: Immunochemical 'activity' without clinical expression. *Int Arch Allergy Appl Immunol* 1980;61:286-292.

Hory B, Haultier JJ: Glomerulonephritis and hereditary angioedema: Report of 2 cases. *Clin Nephrol* 1989;31:259-263.

Pan CG, Strife CF, Ward M, Spitzer RE, McAdams AJ: Long-term follow-up of non-systemic lupus erythematosus glomerulonephritis in patients with hereditary angioedema: Report of four cases. *Am J Kidney Dis* 1992;19:526-531.

Habib R, Loirat C, Gubler MC, et al: Morphology and serum complement levels in membranoproliferative glomerulonephritis. *Adv Nephrol* 1974;4:109-136.

10 Schifferli IA; Ng YC, Peters DK: The role of complement and its receptors in the elimination of immune complexes. *N Engl J Med* 1986;24: 315-317.