Hereditary Angioedema Complicated with Chronic Renal Failure: Report of Sibling Cases

Hideki NOMURA, Yoshinori TSUGAWA, Ichiro KONI, Yohei TOFUKU, Hiroshi MABUCHI, Ryoyu TAKEDA and Takashi SATO*

Hereditary angioedema (HAE) is known as a deficiency state of C1 inhibitor (C1 INH), an important protease inhibitor protein involved in the complement system. As with other components of the classical pathway of the complement system, a state of its deficiency often causes clinical immunoregulatory disorders. A 45-yr-old brother and a 63-yr-old sister with HAE both developed chronic renal failure, probably due to chronic glomerulonephritis, and required regular hemodialysis. This is, to our knowledge, the first report of sibling cases of HAE associated with chronic renal failure.
(Internal Medicine 31: 94–97, 1992)

Key words: C1 inhibitor (C1 INH), hemodialysis

Introduction

Hereditary angioedema (HAE) was first reported by Osler (1) in 1888 as an inherited disease presenting with chronic intermittent attacks of transient swelling in various parts of the body. In 1963, Donaldson and Evans (2) demonstrated a deficiency of C1 inhibitor (C1 INH) protein in the plasma of patients with HAE. HAE is now recognized as one of the most common genetically linked disorders involving the complement system.

There have been many reports of autoimmune diseases in association with congenital deficiencies of classical pathway components. Here we report sibling cases of HAE complicated with chronic renal failure which was considered to have resulted from glomerulonephritis.

Case Reports

Case 1

A 45-yr-old Japanese man had suffered from recurrent, self-limited attacks of non-pitting edema in various regions of the body, including the fingers, hands, forearms, legs, hips and genitals, lips, tongue and throat since the age of 14, and also occasional acute attacks of abdominal fullness. Although the attacks occurred only once a year until the age of 23, they gradually increased in frequency to once a month before his introduction to regular hemodialysis. Proteinuria had been detected at the age of 18, but he received no medical treatment until the age of 39, when he complained of dizziness, at which time the blood pressure was 240 mmHg systolic and 170 mmHg diastolic. Soon after admission, hemodialysis treatment was begun because of severe azotemia (serum urea nitrogen 84.3 mg/dl, serum creatinine 13.0 mg/dl) and anuria.

Although the frequency of swelling attacks increased to once a week after the initiation of hemodialysis, the degree of swelling became milder. During the 6 yr on hemodialysis, he experienced three episodes of arteriovenous fistula obstruction. In March 1989, he was transferred to our hospital for initiation of continuous ambulatory peritoneal dialysis (CAPD) therapy. By this time, the frequency of swelling attacks had decreased to about once every 3 months.

Investigation revealed that the serum C4 concentration was undetectable (<5 mg/dl), C1 INH was reduced to 9.8 mg/dl, C3 and C1q levels were normal (108 and 4.2 mg/dl, respectively), whereas, in three other patients undergoing regular hemodialysis, the levels of serum C1 INH, C3 and C1q were 35.5 ± 10.2, 86 ± 22, 9.6 ± 1.2 mg/dl, respectively. Serum urea nitrogen and creatinine levels were as high as 90 and 12.1 mg/dl, respectively. Rheumatoid factor was weakly positive, 52 IU/ml, but both antinuclear antibodies and anti-DNA antibodies

From The Second Department of Internal Medicine, School of Medicine, Kanazawa University and *The Department of Internal Medicine, Ishikawa Prefectural Central Hospital, Kanazawa
Received for publication June 6, 1990; Accepted for publication May 10, 1991
Reprint requests should be addressed to Hideki Nomura, MD, The Second Department of Internal Medicine, School of Medicine, Kanazawa University, Takara-machi 13-1, Kanazawa 920, Japan

were negative. C1q binding immune complex was undetectable in the serum. These results and the previous clinical history were compatible with a diagnosis of HAE.

No particular prophylactic treatment for the attacks was deemed necessary considering the low frequency and mildness of his angioedema attacks. CAPD catheter implantation was performed, soon after which, however, the effluent became hypercoagulative, and catheter tip malposition was observed on abdominal roentgenogram. The catheter was removed on the 7th day after placement because of fibrin clot. Hemodialysis was again performed using a re-established arteriovenous fistula under 2,000 U of heparin sulfate at the start of dialysis and 1,500 U every hour as an anticoagulant.

Angioedema attacks were observed once after catheter implantation and twice after the arteriovenous shunt operation. The data during the periods with and without angioedema are shown in Fig. 1. Serum C1 INH, C1q, and C4 levels were elevated to normal concentrations during the angioedema attacks (31.3, 17.0 and 13.5 mg/dl, respectively). The angioedema disappeared after the infusion of a total dose of 50 mg of nafamostat mesilate, a serine protease inhibitory agent, at the time of the third angioedema attack (Fig. 2). At present, he is undergoing maintenance hemodialysis and receiving an oral dose of 750 mg/day of tranexamic acid with no further angioedema attacks.

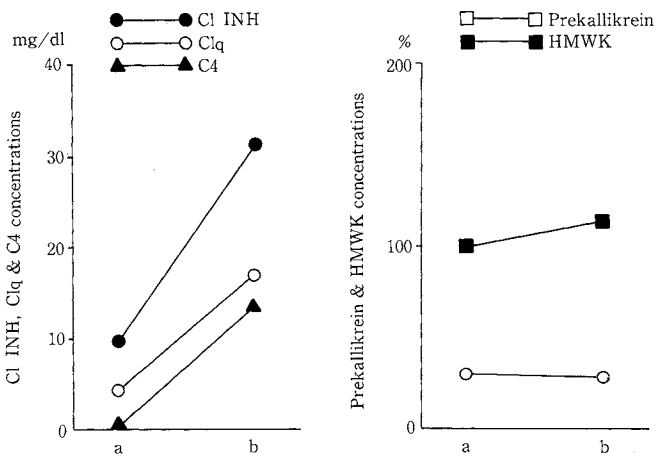

Fig. 1. Changes in serum C1 INH, C1q, C4, prekallikrein and high molecular weight kininogen (HMWK) concentrations without (a) and with (b) angioedema attack.

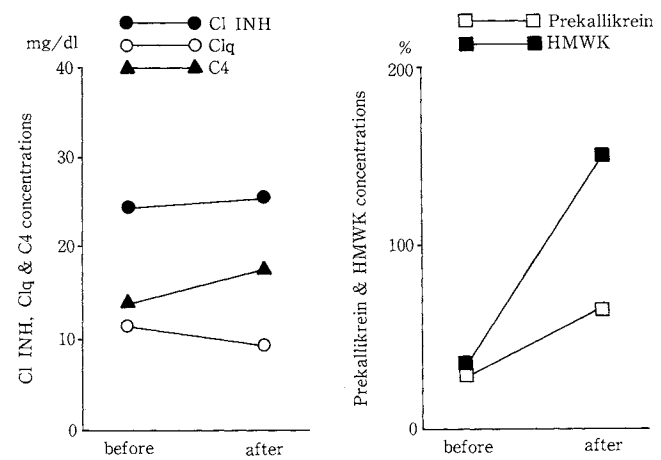

Fig. 2. Changes in serum C1 INH, C1q, C4, prekallikrein and high molecular weight kininogen (HMWK) concentrations with 50 mg infusion of Nafamostat Mesilate.

Case 2

The 63-yr-old sister of case 1 had a history of recurrent swelling of the extremities, and occasionally the lips, from the age of 20. Hypertension without any particular symptoms was incidentally detected at the age of 51, but was untreated. When proteinuria was pointed out at the age of 57, she was already suffering from chronic renal failure. She was admitted to Ishikawa Prefectural Central Hospital and began regular hemodialysis therapy when she was 59 yr old after creation of an internal arteriovenous shunt on her left forearm. The frequency of angioedema attacks increased for several weeks, and became more frequent after the initiation of hemodialysis. The attacks characteristically appeared on the day after each hemodialysis session on her left arm, and occasionally on her lips and face.

Laboratory findings at the age of 63, when she was receiving regular hemodialysis, were as follows: decreased serum C4 concentration to 5.9 mg/dl, normal level of C3 as high as 56.2 mg/dl, slightly decreased C2 level to 1.2 mg/dl, decreased C1 INH to 14.4 mg/dl. Serum C1q binding immune complex was positive, 2.7 g/ml. Rheumatoid factor, anti-DNA antibodies and antinuclear antibodies were negative. The diagnosis of HAE was made because she had a history and clinical features similar to those of her brother.

She is at present being treated with 1,500 mg of tranexamic acid a day and is alomst free from angioedema attacks. She has fortunately experienced no obstructions of her arteriovenous fistula, although her brother had to receive several surgical interventions because of arteriovenous shunt obstruction.

Regarding the family, the patients' parents and the other six siblings are free from both angioedema attacks and immunoregulatory disorders according to our two patients' depositions although permission for familial study was regretfully not obtained. Case 1 is childless. Case 2 had a son and two daughters, one of whom died of unknown causes at a young age. The other daughter, son, and other relatives are free from angioedema attacks.

Discussion

C1 INH is a protease inhibitor involved in the regulation of the complement system, as well as coagulation, fibrinolytic and contact (kinin-kallikrein) systems. Although

the mechanism of angioedema remains unknown, HAE is a disorder associated with C1 INH deficiency, and characterized by recurrent angioedema attacks involving the upper airway, tongue, gastrointestinal tract, face, extremities, and other parts of the body.

HAE is classified into three types (3, 4). Type I HAE, the most common, is characterized by a low concentration of serum C1 INH. Types II and III are characterized by a normal or slightly elevated concentration of a dysfunctional C1 INH protein which can be electrophoretically differentiated. The present two cases showed a decreased concentration of plasma C1 INH to 38 and 30% of the mean concentration in hemodialysis controls. These results are compatible with type I HAE.

One function of the complement system is the disposal of immune complexes, mediated by complex release activity and prevention of immune precipitation *in vitro* (5). Recent studies have revealed that the classical pathway of the complement system plays some role in the early phase of complex release and also a major role in the prevention of immune precipitation, suggesting that deficiencies of some components of the classical pathway of the complement system may be associated with immunoregulatory disorders. It is thought that decreased levels of serum C1 INH are insufficient to inhibit the deposition of immune complexes in target organs such as the kidney, whereas such levels are adequate to inhibit the autoactivation of C1 in the non-angioedemic state.

The first case of HAE associated with glomerulonephritis was reported by Pickering et al (6) in 1971, who found basement membrane thickening, centrilobular and glomerular hyalinization, mesangial proliferation and interstitial round cell infiltration. The second case described by Peters et al (7) in 1973 presented with type II membranoproliferative glomerulonephritis with positive C3 nephritic factor in the plasma. D'Amelio et al (8) commented on a case of HAE and chronic membranoproliferative glomerulonephritis in 1986. In the same year, Brickman et al (9) found 5 cases of glomerulonephritis in a series of 157 patients with HAE, and documented that 12% of the HAE patients in their series had associated autoimmune disorders including glomerulonephritis. The first case of Hory and Haultier (10) in 1989 showed diffuse proliferative glomerulonephritis with scattered wire loop lesions on renal biopsy. The second case showed type I membranoproliferative glomerulonephritis with immune complexes present in the plasma. One case of Brickman et al (9) and two cases of Hory and Haultier (10) were described as receiving hemodialysis but no further information about the hemodialysis procedure itself, such as anticoagulant usage, is available. In the present two cases, the underlying cause of the chronic renal failure was presumed to be chronic glomerulonephritis based on their histories of long-standing proteinuria, although renal biopsy examinations were not performed. The presence of rheumatoid factor in case 1 and immune complexes in case 2 also support this presumption.

The serum concentrations of classical pathway components of the complement system in hemodialysis patients have been studied in only a few reports, although some reports have estimated C3 concentrations in hemodialysis patients (11). Jorgensen and Stoffersen (12) described that there were no statistically significant differences in C1q, C1 INH and C4 concentrations among hemodialysis patients, conservatively treated chronic renal failure patients and healthy controls. There are several problems in evaluating C1 INH concentrations in hemodialysis patients. First, it is necessary to estimate the influence of heparin on serum C1 INH concentration, because heparin potentiates C1 INH activity. Also, many other factors may affect C1 INH function in hemodialysis patients; for example, inhibitory activity of C1 INH to factor XII of the coagulation system may play a role in inhibiting coagulation in contact with the dialyzer membrane. The hemodialysis control subjects ($n = 3$) in the present study exhibited slightly elevated concentrations of C1 INH (normal range: 15–35 mg/dl). C4 concentrations did not differ from those in normal subjects described in previous reports. But in the near future, it will be necessary to consider the possibility that recently described genetic polymorphisms in C2 and C4 (13), and an acquired C4 variant in some uremic patients (14) might modify the plasma concentrations of these complement components.

Changes in the C1 INH, C2 and C4 concentrations during angioedema attacks were not fully investigated in the previous reports. During attacks, C1 INH is considered to be excessively consumed due to inhibition of local activation of the kinin-kallikrein system, resulting in a further decrease of C1 INH. Here, in the first case, C1 INH, C2 and C4 concentrations were elevated during the angioedemic state. Possibly local consumption of C1 INH stimulated the production of this component.

Nafamostat mesilate is a protease-inhibiting agent developed by Fujii and Hitomi (15) in 1981. In case 1, after the infusion of nafamostat mesilate, marked increases in high molecular weight kininogen concentrations and an improvement in the prekallikrein level were found, although no changes in the C1 INH, C1q, C2 or C4 concentrations, which were already within normal ranges, were observed. This biological effect of the drug resulting in inhibition of the activation of the kinin-kallikrein system may result in clinical improvement of angioedema, because the angioedema itself is believed to result from local activation of the system. This drug may lead to some improvement in the treatment of HAE, especially in high risk patients.

In summary, we report sibling cases of HAE complicated with chronic renal failure. The cause of the renal failure was considered to be chronic glomerulonephritis, which may have had some pathogenic correlation with

the C1 INH deficiency. In one case, nafamostat mesilate was effective in the treatment of the acute angioedema attacks, and in both cases tranexamic acid was useful in the prevention of the attacks.

References

1) Osler W. Hereditary angio-neurotic oedema. Am J Med Sci **95:** 362, 1888.
2) Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: Absence of serum inhibitor of C1-esterase. Am J Med **35:** 37, 1963.
3) Rosen FS, Charache P, Pensky J, Donaldson V. Hereditary angioneurotic edema: Two genetic variants. Science **148:** 957, 1965.
4) Donaldson VH, Harrison RA, Rosen FS, et al. Variability in purified dysfunctional C1-inhibitor proteins from patients with hereditary angioneurotic edema: Functional and analytic gel studies. J Clin Invest **75:**124, 1985.
5) Takahashi M, Takahashi S, Hirose S. Solubilization of antigen-antibody complexes: A new function of complement as a regulator of immune reactions. Prog Allergy **27:** 134, 1980.
6) Pickering RJ, Miguael AF, Herdman RC, Good RA, Gewurz H. The complement system in chronic glomerulonephritis; Three newly associated aberrations. J Pediatr **78:** 30, 1971.
7) Peters DK, Charlesworth JA, Sissons JGP, Williams DG, Boulton-Jones JM, Evans DJ. Mesangiocapillary nephritis, partial lipodystrophy and hypocomplementoemia. Lancet **ii:** 535, 1973.
8) D'Amelio R, Perricone R, De Carolis C, Pontesilli O, Matricardi PM, Fontana L. Immune complexes in hereditary angioneurotic edema (HANE). J Allergy Clin Immunol **78:** 486, 1986.
9) Brickman CM, Tsokos GC, Balow JE, et al. Immunoregulatory disorders associated with hereditary angioedema. J Allergy Clin Immunol **77:** 749, 1986.
10) Hory B, Haultier JJ. Glomerulonephritis and hereditary angioedema: Report of 2 cases. Clin Nephrol **31:** 259, 1989.
11) Cheung AK, Henderson LW. Effects of complement activation by hemodialysis membranes. Am J Nephrol **6:** 81, 1986.
12) Jorgensen KA, Stoffersen E. The complement system in uremia. Scand J Urol Nephrol **14:** 279, 1980.
13) Awdeh ZL, Alper CA. Inherited structural polymorphism of the fourth component of human complement. Proc Natl Acad Sci USA **77:** 3576,1980.
14) Welch TR, Beischel L. C4 uremic variant: An acquired C4 allotype. Immunogenetics **22:** 553, 1985.
15) Fujii S, Hitomi Y. New synthetic inhibitors of C1r, C1 esterase, thrombin, plasmin, kallikrein and typsin. Biochem Biophys Acta **661:** 342, 1981.