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A case of Hereditary Angioedema Associated with Idiopathic Hypoparathyroidism

Sang Hoon Kim, M.D., Byung Jae Lee, M.D., Yoon Seok Chang, M.D., Yoon Keun Kim, M.D., Sang Heon Cho, M.D., Kyung Up Min, M.D. and You Young Kim, M.D.

Department of Internal Medicine, Seoul National University College of Medicine; Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul, Korea

Hereditary angioedema is a rare autosomal dominant disease characterized by the edema of subcutaneous tissues, respiratory tract and bowel. It is caused by the deficiency of C1 esterase inhibitor. Hereditary angioedema may be associated with autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroiditis and glomerulonephritis. We report a 34-year-old male patient with hereditary angioedema who developed idiopathic hypoparathyroidism. Autoimmunity seems to be an important basis of this association and it might be caused by the immune dysfunction due to decreased level of complements; nevertheless, a casual association could not be excluded. To our knowledge, this is the first report of hereditary angioedema in association with idiopathic hypoparathyroidism in the medical literature.

Key Words : *hereditary angioedema, hypoparathyroidism, complement*

INTRODUCTION

Hereditary angioedema (HAE) is a rare disease that usually occurs in adolescence and early adulthood. The disease is characterized by the recurrent, self-limited attacks of non-pitting edema. It is not associated with urticaria and pruritus but associated with abdominal complaints. This disease is inherited as an autosomal dominant trait and caused by the deficiency of C1 esterase inhibitor (C1-INH) resulting in activating classic complement pathway[1]. HAE may be associated with autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, autoimmune thyroiditis and glomerulonephritis[2-5]. Idiopathic hypoparathyroidism may be developed by autoimmune mechanism as a part of polyglandular autoimmune syndrome or as an isolated hypoparathyroidism[6-7]. A case of HAE associated with idiopathic hypoparathyroidism has not been reported in the literature. We report a 34-year-old male patient with HAE who developed idiopathic hypoparathyroidism.

Address reprint requests to : You-Young Kim, M.D., Department of Internal Medicine, Seoul National University College of Medicine, 28 Yongondong, Chongnogu, Seoul 110-744, Korea

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CASE

A 34-year-old male visited the emergency room because of involuntary movement of extremities and edema on the hand. He had no history of neck operation, trauma, transfusion and other developmental anomalies. He had suffered, for the last 10 years, from the clinical symptoms of HAE with recurrent, self-limited cutaneous swellings and abdominal pain. One year ago, he had been treated with a mechanical ventilator because of laryngeal edema.

Serologic tests were performed at the emergency room. Serum total calcium, ionized calcium and phosphate levels were 5.8 mg/dL (normal range 8.8-10.5), 0.7 mmol/L (normal range 1.05-1.35) and 5.7 mg/dL (normal range 2.5-4.5), respectively. Parathyroid hormone and 1,25-

OH-vitamin D levels were less than 5 pg/mL (normal range 10-65) and 8.10 pg/mL (normal range 20-60), respectively. C1-INH level and functional activity of C1-INH were 10.2 mg/dL (normal range 15- 35) and less than 25% (normal range 80-125), respectively. C1q, C3, C4 levels and CH50 were 9.15 mg/dL (normal range 12.4-19.0), 77 mg/dL (normal range 70-150), 5 mg/mL (normal range 10-40) and 6.4 (normal range 30-45), respectively. Other serological studies showed no remarkable findings.

To diagnose HAE, the C4 level and functional activity of C1-INH of his family members were measured (Figure 1). His monozygotic twin daughters showed low C4 level and decreased functional activity of C1-INH although they had never experienced clinical symptoms of HAE. On the diagnosis of type I HAE with idiopathic hypoparathyroidism, the patient was treated with calcium replacement and attenuated androgen (danazol) and the clinical manifestations were improved.

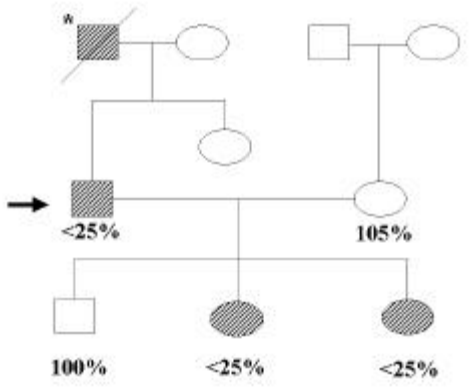

Figure 1. Pedigree of the family. Proband is indicated by an arrow. The percentages represent the functional activities of C1 esterase inhibitor (Open symbol: unaffected, hatched symbol: affected, /: not alive, *: suspected case due to unexplained sudden death).

DISCUSSION

HAE is an autosomal dominant genetic disorder characterized by recurrent swelling of extremity, respiratory tract and bowel. It is caused by the deficiency of serum C1 esterase inhibitor (C1-INH). Two types of deficiency have been described; type 1 with a low level of C1-INH antigen and the rare type 2 with a normal or elevated serum levels of dysfunctional C1-INH[1].

C1-INH plays a central role in the regulation of the complement, coagulation and contact (kinin-forming) systems. As a member of the family of serine protease inhibitors, C1-INH acts as a suicide protein by forming complexes with the target proteases. It inhibits C1r and C1s in the complement system, factor XII and kallikrein in the contact system and factor XI in the coagulation system. Patients with a deficiency of C1-INH have low plasma levels of C4 which is the substrate of the C1r-C1s complex.

It has been reported that patients with HAE have an increased incidence of immunoregulatory or autoimmune diseases[8]. Previous reports have emphasized the striking incidence of systemic lupus erythematosus, as well as membranoproliferative glomerulonephritis, in this patient group[2-4]. In general, patients with HAE have unregulated activation of the early steps of the classic complement pathway with decreased (but not absent) levels of C4 and C2. Decreased or dysfunctional complement may promote the tissue deposition of immune complexes and autoimmue disease because complement proteins play an important role in the clearance of immune complexes or autoantibodies.

Hypoparathyroidism may develop as a solitary endocrinopathy which is called isolated or idiopathic hypoparathyroidism. Idiopathic hypoparathyroidism is sometimes associated with developmental anomalies, such as dwarfism, cortical thickening of tubular bones, nephropathy, sensorineural deafness and lymphedema. It has been reported that several genetic defects are associated with the development of idiopathic hypoparathyroidism[9]. Most of adult-onset idiopathic hypoparathyroidism may be developed by the mechanism of autoimmune basis[6, 7, 10]. The association with other autoimmune disease is well established and the presence of autoantibodies to parathyroid cells provides further circumstantial evidence of an autoimmune etiology[11].

In our case, we can assume that HAE might be associated with hypoparathyroidism, as well as systemic lupus erythematosus, because of the genetically determined dysfunction of complement pathway. A casual association could not be excluded and further studies are needed to elucidate the detailed mechanism of these immune-based diseases.

REFERENCES

1. Cicadi M, Agostoni A. Hereditary Angioedema. N Med J Med 334:1666-7, 1996

2. Gudat W, Bork K. Hereditary Angioedema associated with subacute cutaneous lupus erythematosus. Dermatologica 179:211-3, 1987
3. Hory B, Haulhier JJ. Glomerulonephritis and hereditary angioedema: report of 2 cases. Clinical Nephrology 31:259-63, 1989
4. van Bommel EFH, Ouwehand AJ, Mulder AH, Weimar W. Mesangiocapillary Glomerulonephritis Associated with Hereditary Angioedema. Nephron 69:178-9, 1995
5. Muhlemann MF, Macrae KD, Smith AM, Beck P, Hine I, Hegde U, Milford-ward A, Carter GD, Wise PH, Cream JJ. Hereditary angioedema and thyroid autoimmunity. J Clin Pathol 40:518-23, 1987
6. Rose N. Is Idiopathic hypoparathyroidism an autoimmune disease? J Clin Invest 97:899-900, 1996
7. Weetman AP. Autoimmunity and endocrinology. Exp Clin Endocrinol Diabetes 107:S63-6, 1999
8. Brickman CM, Tsokos GC, Balow JE, Lawley TJ, Santaella M, Hammer CH, Frank MM. Immunoregulatory disorders associated with hereditary angioedema: 1. Clinical manifestations of autoimmune disease. J Allergy Clin Immunol 77:749-57, 1986
9. Trump D, Dixon PH, Mumm S, et al. Localisation of X linked recessive idiopathic hypoparathyroidism to a 1.5 Mb region on Xq26-q27. J Med Genet 32:905-9, 1998
10. Salvador G, Sanmarti R, Ros I, Halperin I, Canete JD, Orellana C, Murinoz-Gomez J. Idiopathic hypoparathyroidism associated with adult rheumatoid arthritis. Clin Rheumatol 18:334-6, 1999
11. Posillico JT, Wortsman J, Srikanta S, Eisenbarth GS, Mallette LE, Brown EM. Parathyroid cell surface autoantibodies that inhibit parathyroid hormone secretion from dispersed human parathyroid cells. J Bone Miner Res 1:475-83, 1986