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Case Report

Successful treatment of post-pericardiotomy syndrome via C1 inhibitor replacement therapy in a hereditary angioedema patient with Marfan syndrome

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ABSTRACT

Background. Hereditary angioedema with C1 inhibitor deficiency (HAE-C1INH) is caused by dysfunctional C1-INH protein due to mutations in the *SERPING1* gene encoding C1-INH. Marfan syndrome is a genetic connective tissue disease that affects the cardiovascular and ocular systems along with the skeletal system. In this case, we present the successful treatment of post-pericardiotomy syndrome unresponsive to classical therapy, which has not been described in the literature. The syndrome developed in a patient with hereditary angioedema (HAE) who underwent open heart surgery due to cardiac involvement in Marfan syndrome.

Case. A nine-year-old male HAE-C1INH patient underwent open heart surgery secondary to cardiac involvement caused by Marfan syndrome. To prevent HAE attacks, 1000 units of C1 inhibitor concentrate therapy were given 2 hours before and 24 hours after the operation. Post-pericardiotomy syndrome was diagnosed on the postoperative second day and ibuprofen 15 mg/kg/day (3 weeks) was started. Since there was no response to classical treatment on the 21st postoperative day, C1 inhibitor concentrate treatment was planned as 1000 units/dose for 2 days a week considering a prolonged hereditary angioedema attack. In the second week of treatment, complete recovery was achieved for pericardial effusion with a total of 4 doses.

Conclusions. We emphasize that in patients with hereditary angioedema undergoing this treatment, care should be taken in terms of complications that may be associated with the disease even if short-term prophylaxis is given before operations and that longer-term use of C1 inhibitor concentrate has a place in treatment.

Key words: hereditary angioedema, Marfan syndrome, post-pericardiotomy syndrome, C1 inhibitor replacement therapy.

Hereditary angioedema (HAE) is a rare potentially life-threatening autosomal dominant disease characterized by episodes of cutaneous and submucosal edema. It is estimated to occur at a rate of 1/50,000 that varies in different regions.[1-3] The main abnormality is a deficiency/defect of C1 inhibitor (C1-INH) protein or other mechanisms. Genetically identifiable forms of hereditary angioedema (HAE) are listed in Table I. The genetic defects in Type 1 and Type 2 are mutations in the *SERPING1* gene, which encodes the functional C1-INH protein that regulates multiple proteases involved in the complement contact system, coagulation, and fibrinolytic pathways.[2] However, de novo mutation of *SERPING1* is responsible for the disease in approximately 20-25% of patients. Type I HAE is present in 85% of patients and type II HAE affects the remaining 15%.[4,5]

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Table I. Genetically identifiable forms of HAE

Type of HAE	Underlying defect
HAE-1 (Type 1 HAE)	C1-INH deficiency (low antigenic and functional C1-INH levels
HAE-2 (Type 2 HAE)	C1-INH dysfunction (normal or elevated antigenic but low functional C1-INH levels)
HAE-FXII	Mutation in the factor XII gene
HAE-ANGPT1	Mutation in the angiopoietin-1 gene
HAE-PLG	Mutation in the plasminogen gene
HAE-KNG1	Mutation in the kininogen 1 gene
HAE-MYOF	Mutation in the myoferlin gene
HAE-HS3ST6	Mutation in the heparan sulfate 3-O-sulfotransferase 6 gene
HAE-UNK	Patients without known mutations have been described.

C1-INH: C1-inhibitor, HAE: hereditary angioedema

Cutaneous edema attacks are the most common symptoms and occur in >95% of patients. Patients often experience recurrent abdominal pain caused by bowel wall angioedema. Laryngeal edema is the most serious complication seen in 50% of patients and can be life-threatening if not treated promptly. Symptoms are usually self-limiting and progress within hours, with the frequency of attacks ranging from once a week to several attacks per year.[6-8] Although its clinical manifestations usually begin in the first and second decades of life, delay in accurate diagnosis and the inadequacy of effective therapeutic approaches have hindered effective management of the disease until recently. With the introduction of C1 inhibitor concentrations, successful results were obtained from both short-term and long-term prophylaxis of HAE attacks and acute attack treatment.[2]

Marfan syndrome (MFS) is a genetic connective tissue disease that affects the cardiovascular and ocular systems along with the skeletal system. It is characterized by a qualitative/quantitative disorder of fibrillin synthesis as a result of a defect in the fibrillin gene (*FBN1*) on chromosome 15.[9] In this case, we present a previously unreported association of Marfan syndrome and hereditary angioedema, as well as the successful treatment of post-pericardiotomy syndrome unresponsive to classical ibuprofen therapy.

Case Report

A 9-year-old male patient was admitted to an external center due to recurrent penile/testicular swelling that started at the age of 4 years. Since his father had a diagnosis of HAE type 2, examinations about C1-INH were as follows: C1-INH level: 72.3 mg/dl (n:21-39), C1-INH activity: 27.4% (n:70-130), C4: <6.65 mg/dl (n:10-40). On genetic examination, a heterozygous p.Arg466Cys (c.1396C>T) mutation was detected in *SERPING1*, and he was diagnosed with HAE Type 2. In addition, aortic root dilatation, mitral valve prolapse, and mitral insufficiency were detected in the postnatal 6th month, and genetic examination revealed heterozygous p.Gly1226Val (c.3677G>T) mutation in the 29th exon of the *FBN1* gene, and a diagnosis of Marfan syndrome was made. The patient, who was planned to have open heart surgery with the Bentall procedure (because of the risk of perforation of the aortic valve that may be caused by excessive enlargement of the aortic diameter), was admitted to our hospital's pediatric allergy clinic 4 months prior for management of the process and the follow-up of the disease. According to the HAE on-demand treatment protocol, 1000 units of C1-INH concentrate treatment was applied for 2 hours before the operation and in the 24th hour after the operation. In addition, 3 units of fresh frozen plasma (FFP) were administered during the operation which lasted for a total of 6 hours,

165 minutes of which was on cardiopulmonary bypass. During intubation and extubation, no complication was seen. On the second day after the operation, echocardiography revealed posterior pericardial fluid and post-pericardiotomy syndrome was considered. Ibuprofen 15 mg/kg/day (3 weeks) and colchicine 1 mg/kg/day were started. As pericardial fluid did not decrease on the 21st postoperative day, prolonged hereditary angioedema attack could not be excluded. C1-INH concentrate treatment was planned as 1000 units/dose for 2 days/week. Pericardial fluid regression was observed on the control echocardiography at the end of the first week and the treatment was continued. Complete recovery was achieved for pericardial effusion with a total of 4 doses. Informed consent was obtained from the family for the publication of the case report.

Discussion

Marfan syndrome, a systemic disorder of connective tissue, is a disease with a wide phenotypic spectrum associated with heterozygous *FBN1* pathogenic variants. In MFS, there are mainly ocular, skeletal and cardiovascular system involvements. Major morbidity and early mortality in MFS are related to the cardiovascular system; dilatation of the aorta at the level of the sinuses of valsalva, mitral and tricuspid valve prolapse, and enlargement of the proximal pulmonary artery may be seen. Stretching of the aortic valve annulus due to aortic root enlargement can cause leaflet faulty coaptation and aortic valve regurgitation. In pediatric patients with MFS, moderate to severe aortic valve regurgitation was found to be a predictor of aortic root enlargement and cardiovascular events such as death and aortic dissection. Aortic valve insufficiency has become an important feature in prophylactic surgery indications with the introduction of valve-sparing aortic root replacement techniques.[10,11]

The classical complement, coagulation cascade and antifibrinolytic systems are inhibited by the C1 esterase inhibitor. Failure to prevent complement activation leads to increased production of C2 kinin and bradykinin. The released substances induce endothelial cell retraction in the post-capillary venules, causing cavities and plasma leakage, leading to angioedema. Hereditary angioedema associated with a hereditary deficiency of C1 esterase inhibitor is characterized by recurrent episodes of painful swelling in the subcutaneous and/or submucosal tissues.[8]

There are three different types of management in the treatment of C1-INH-deficient HAE: on-demand therapy (during acute attacks), management of attacks with short-term or procedural prophylaxis, and long-term prophylaxis. Most drugs used in the treatment of HAE are not approved for use in children, and data about safety and efficacy are lacking. Therefore, plasma-derived C1-INH was recommended as first-line therapy for short- and long-term prophylaxis, as well as for the treatment of acute attacks in children.[2]

HAE attacks are often unpredictable, but a dental or medical procedure such as surgery, trauma, or stress is known to be a trigger for an attack. A preventive management plan before such situations can reduce the risk of HAE attacks. The probability of angioedema attack increases up to 30% after a surgical procedure without prophylaxis.[12] In addition, surgery and cardiopulmonary bypass (CPB) are known to activate the complement cascade and increase the risk of angioedema.[13] Tanaka et al.[14] reported data on 13 patients with type 1/2 HEA who underwent cardiac surgery, 7 of them received preoperative C1-INH supplementation. No cardiac complications were observed in any of these patients. Only one patient had swelling in the lower back and lips on the 2nd postoperative day, treated with 1000 IU of C1-INH as a precaution, and these symptoms resolved

within 2 hours.[15] Preoperative replacement with C1-INH (1000 IU or 20 IU/kg) 1-6 hours before major surgery is recommended. It is known that plasma C1-INH activity increases by 2.2% for every 1 IU/kg. Theoretically, although the actual efficacy among HAE patients is highly variable, the reported C1-INH activity after one dose of C1-INH (1000–1500 IU) appears to be consistent with its pharmacokinetics.[13,14] Cardiovascular surgery and CPB may affect intraoperative C1-INH activity after preoperative replacement. The C1-INH level is affected not only by the plasma half-life of each product, but also by the kallikrein-kinin system, complement activations and contact coagulation after initiation of CPB. Ongoing bleeding, fluid replacement, and blood administration (other than plasma) can progressively reduce C1-INH activity. C1-INH activity decreases by 30-50% from baseline after CPB. Postoperative supplementation of C1-INH may be considered if low-grade bradykinin formation persists and a delay in classical pathway activation occurs 24-48 hours after surgery.[16]

In the literature, there was a patient with aortic aneurysm who developed ascites, hypovolemic shock, and acute renal failure following a HAE abdominal crisis triggered by spontaneous retroperitoneal bleeding. Although this patient received renal dialysis, assisted ventilation, blood transfusions, daily danazol (200 mg) and intermittent C1-INH concentrate, good clinical response could not be obtained. For this reason, daily C1-INH concentrate was applied for 21 days (1000 units per day). After 4 days of C1-INH treatment, renal functions, abdominal ascites, and pneumonia also clinically improved gradually.[17]

Prolonged HAE attack terminology has not yet been used in the literature. HAE symptoms are generally worse during the first 24 hours and gradually subside in severity over the following 2 to 5 days. We used prolonged HAE attack terminology in our case report since there was no response to classical treatment for post-pericardiotomy syndrome on the 21st postoperative day. However C1 inhibitor concentrate treatment of 1000 units/dose for 2 days a week resulted in complete recovery of pericardial effusion with a total of 4 doses. We assume overactivation of complement cascade and factor XII due to the usage of heparin-protamine complexes during cardiac surgery.[13] In addition, ongoing bleeding and fluid replacement may progressively reduce C1-INH activity. C1-INH activity decreases by 30-50% from baseline after CPB.[16] On the other after tissue injury, damage-associated molecules, such as S100 and the high mobility group box 1 (HBGM1) proteins, defensins, lectins, cardiolipin, cellular DNA and dsRNA, and even intact mitochondria, occur in the extracellular microenvironment. Interaction of these molecules with multiligand receptors, activate the cellular and molecular effector mechanisms of the innate immune system, including activation of the clotting and complement system, acute phase protein and pentraxin production, and the cellular inflammatory responses. It means that there is more complement activation in patients with C1 inhibitor deficiency, as in our patient. However, in experimental, studies C1 inhibitor concentrate improves healing and re-epithelialization.[18] Inadequate wound healing especially in cardiac surgery may lead to the presence of cell residues that cause continuous complement activation in HAE patients and may prolong the HAE attack.

In our case, although he received both preoperative prophylaxis and postoperative C1-INH treatment, post-pericardiotomy syndrome developed, and there was no response to ibuprofen and colchicine treatment. Since prolonged hereditary angioedema attack could not be excluded, C1-INH concentrate treatment was given and pericardial effusion was completely resolved with 4 doses. Our patient is the first case in the literature who developed post-pericardiotomy syndrome despite having received both preoperative prophylaxis and postoperative C1-INH. On the other hand, a different treatment modality was attempted and achieved successful results.

At the same time, this is the first case with two orphan diseases, HEA and Marfan syndrome, in the literature.

In conclusion, in patients with hereditary angioedema, care should be taken in terms of complications that may be associated with the disease even if short-term prophylaxis was given before an operation, and the necessity of longer-term administration of C1 inhibitor concentrates in treatment should be kept in mind.

Ethical approval

Informed consent was obtained from the family for the publication of the case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: NMG, ET; data collection: HDS; analysis and interpretation of results: ED, FG, HDS; draft manuscript preparation: NMG, ET. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

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