Localized edema of the larynx and pharynx leading to death from asphyxia has long been recognized as a characteristic symptom of hereditary angioneurotic edema (HANE). Long-term follow-up of younger HANE patients has revealed that transient localized acute attacks of edema affect tissues where the microcirculation maintains the blood supply. However, with aging, HANE attacks precipitate disseminated intravascular coagulation (DIC) or multiple organ failure (MOF). Substitution with a C1-inhibitor (C1-INH) has resulted in a fulminant lethal end with a rapid and profound decrease in antithrombin-III (AT-III) activity. A possible mechanism is as follows: Exogenous stimuli activate plasma proteinase systems with the generation of plasma kallikrein that activates the tissue factor pathway (TF) and liberates bradykinin (BK). In younger patients, BK enhances vascular permeability. In the elderly, activated TF is controlled by tissue factor pathway inhibitor (TFPI) and generates thrombin, which is the target enzyme of AT-III and precipitates DIC or MOF. In elderly patients, the characteristic symptom of HANE is hypercoagulation by age-related changes in the biosynthesis of AT-III or TFPI.

(International Medicine 37: 440-443, 1998)

Key words: In vivo C1-inhibitor (C1-INH) function, pathophysiology of hereditary angioneurotic edema (HANE), symptoms of elderly HANE patients, hypercoagulation

Introduction

In 1962, Landerman et al (1) demonstrated that the congenitally deficient plasma factor in patients with hereditary angioneurotic edema (HANE) is the inhibitor of plasma kallikrein. Prior to that work, Landeman (2) had reported on HANE patients and had reviewed other cases described in the literature (3). From the viewpoint of inheritance and clinical outcome, he emphasized that edema of the larynx and pharynx leading to death from asphyxia was the characteristic, but uncommon symptom of this disease. In 1963, Donaldson and Evans (4) demonstrated that the congenitally deficient plasma factor in this disease was C1-inhibitor (C1-INH). In the same year, Kagan and Becker (5) proved that Landerman’s kallikrein inhibitor corresponded to C1-INH. In 1969, Donaldson et al (6) had subsequently postulated that C2-kinin (7, 8) was the permeability-enhancing substance generated in acute HANE attacks. Because a C1-INH preparation has become clinically available (9–11), we assessed the in vivo function of this protein in acute HANE attacks. We demonstrated that its foremost function is inhibition of plasma kallikrein to generate bradykinin, which corresponds with HANE-kinin (12–15). At present, C1-INH is recognized as the regulator protein for the contact phase of the intrinsic coagulation cascade (16, 17), Hageman factor (HF) homologue. In the activation of HF homologue, interactions between plasma proteinase systems occur (16–25). Consequently, biologically active polypeptides are liberated, resulting in the activation of cells in the blood and in the vascular endothelium (21–25). In addition, the chief target tissues for edema attacks in HANE patients (3) are those where blood supply is maintained by the microcirculation. In 1960, Spaulding (26) demonstrated that methyltestosterone can maintain male HANE patients in remission, although gynaecomastia (27) develops. At present, the attenuated androgen, danazol (28), has proved to be useful for both sexes. Furthermore, Frank et al (29) pointed out that oral contraceptives can elicit acute attacks in younger female HANE patients. We (14, 15) have also demonstrated that blood levels of estrone and estradiol modulate the
frequency and severity of edema attacks in female HANE patients and that both hormones are elevated in male patients in remission. Although the effects of female sex hormones on the circulatory system are still controversial (30), these hormones can regulate a number of catecholamine receptors in target organs (31, 32). In addition, Donaldson and Evans (4) reported that amphetamines elicit edema attacks in HANE patients. Furthermore, it has also been postulated that reactions mediated via the hypothalamoneurohypophyseal axis (19, 20) and via catecholamine release can modulate the activation of plasma proteinase systems (33). Therefore, HANE appears a useful model for analyzing the role of the autonomic nervous system and endocrine system in modulating activation of the plasma proteinases, especially in microcirculation.

On the basis of such pathophysiological findings, HANE patients can now be maintained in remission by synthetic inhibitors of activated plasma proteinase systems together with attenuated androgens (29). This has allowed them to survive long enough to evaluate the effects of aging on individuals under medical supervision, especially on female patients. Therefore, we continued clinical follow-up to determine whether the symptoms of acute attacks in female HANE patients actually change with aging. We found that aging altered the features of acute attack of HANE from the occurrence of classical transient localized edema and/or colicky pain to the existence of a hypercoagulable state of the blood. In the present communication, in comparison with the younger female HANE case reported by Mineshita et al (34), we discuss how the classical transient localized edema seen in younger patients changes into a hypercoagulable state in the elderly.

Patients and Methods

Two elderly female patients

Died while being follow-up to evaluate age-dependent changes in the symptoms of acute attacks of HANE. The older one was in remission for nearly 20 years on oral tranexamic acid (tAMCHA) and danazol (100 mg once daily p.o.). After an acute attack of ileus-like colicky pain, she showed symptoms of acute renal insufficiency, became unconscious, and soon died. The other patient suffered from acute circulatory shock, presumably caused by gram-negative bacterial infection. She had edema of the pharynx and larynx, anuria, and neuropsychiatric symptoms after treatment of her circulatory shock, also resulting in a fulminant lethal course.

Methods

In case No. 1, the coagulation status underwent emergency assessment, with inhibitory activity of Cl-INH and antithrombin-III (AT-III) being assayed automatically using a Cobas Fara (35). In the second patient, progression was so rapid after the occurrence of edema that measurement of the coagulation cascade could not be performed.

Case Reports

Case No. 1

A 67-year-old woman had her first attack of edema in the extremities at 15 years of age. At age 17, she had edema of the face and episodes of frequent colicky pain. These ileus-like attacks and severe colicky pain always resolved without any specific treatment. At age 47, she injured her gums, resulting in edema formation in the mouth. This acute attack was treated with Cl-INH concentrate. On the basis of the subsequent changes in the clinical and biochemical parameters, we concluded that Cl-INH functions in vivo as a plasma kallikrein inhibitor and that HANE-kinin corresponds to bradykinin. Since then, she was maintained in remission on oral tAMCHA and danazol, with the exception of edema formation in the soft tissues elicited by compression. Her last and fatal acute attack started in the morning of July 16, 1990 with ileus-like symptoms following overeating on the previous night. In the morning of July 17, anuria occurred and she was admitted to the Emergency Center of Senri near Osaka. In the afternoon, the blood level of Cl-INH was 15%, so 1,500 units of a Cl-INH preparation was given intravenously and the inhibitory activity recovered to 77%. However, the AT-III activity was found to be 55% at the same time. In the afternoon of July 18, she lost consciousness and activity of AT-III decreased to 35% (36). In the evening, she died after a fulminant course of 50 hours from onset.

Case No. 2

A 53-year-old woman was diagnosed as HANE at age 48 by a family study. She had suffered from acute attacks of edema of the extremities at a young age, but had remained in remission after menopause without any specific medication. In mid-December 1990, she suffered from severe influenza and lost her appetite. On December 22, her consciousness became cloudy and in the night of December 23 she went into shock. She was admitted to SaiSeikai Izumo Hospital as an emergency patient. On admission, the blood pressure was 80/46 mmHg, the pulse rate was 96/min, and her temperature was 35.9°C. She could answer questions, but was hypokinetic. There were no neurological signs and no specific findings on physical examination. Radiological examination of the chest and abdomen, computed tomography of the brain and electrocardiogram (ECG) were not helpful. Ultrasound of the abdomen showed a silent gall stone. There was leukocytosis (24,200/c mm) and the hematocrit was 39%. Biochemical data were as follows: aspartate aminotransferase (AST), 190 KU; alanine aminotransferase (ALT), 504 KU; lactate dehydrogenase (LDH), 4,350 IU/l; creatine phosphokinase (CPK), 194 IU/l; creatinine, 3.8 mg/dl; and blood ammonia, 52 µg/dl. Fluid infusion elevated the blood pressure to 110/76 mmHg. However, her consciousness became worse with the onset of agitation. In the morning of December 24, she had hypotension, respiratory distress, and edema of the pharynx and larynx as well as of the neck and the biochemical parameters had worsened (AST, 5,295; ALT, 3,955; LDH, 3,820;
In human umbilical vein endothelial cells cultured with various thromboembolic human diseases. As observed in our case 1, a slight decrease of AT-III appears analogous to the phenomena observed during remission of our younger patients (12). The main difference between our case 1 and the case of Mineshita et al (34) was the rapid and profound decrease of AT-III, which was not improved by C1-INH and was soon fatal (36). Our case 2 and Mineshita's case developed an acute attack in the course of treatment for bacterial infection or circulatory shock. Lipopolysaccharide (LPS) (37) released by gram-negative bacteria and catecholamine derivatives (19, 20, 33) used to treat circulatory shock can activate Hageman factor homologue. Although Mineshita's case (34) improved with gabexate mesilate alone, our second case died of DIC/MOF despite treatment with a C1-INH preparation and gabexate mesilate. The fatal and lethal course observed in our case 2 was probably attributable to her age. On the other hand, the profound and rapid decrease in AT-III activity observed in case 1 may have been the result of wasting or changes in the biosynthesis of AT-III. Gjønnaess (38) has demonstrated in women taking oral contraceptives a phenomenon termed "cold promoted activation of factor VII", involving activation of factor VII by plasma kallikrein (39). We have postulated that the first step in triggering acute attacks of HANE is activation of HF homologue and/or activation of blood cells by infection or disturbances of blood flow (40). Activated blood cells release various cytokines. Also, as emphasized by Morita (41) and Sekiya et al (42), thrombin generation through activation of the tissue factor pathway is much more rapid than through activation of the contact phase of the intrinsic coagulation cascade. In addition, Ameri et al (43) recently reported that expression of tissue factor (TF) mRNA precedes that of tissue factor pathway inhibitor (TFPI) mRNA in human umbilical vein endothelial cells cultured with various cytokines, such as LPS, platelet-activating factor, interleukin-1, and tumor necrosis factor. Furthermore, Katoh (44) emphasized recently that TFPI participates in the development of thromboembolic human diseases. As observed in our case 1, a C1-INH preparation did not improve the clinical status of acute HANE attack and there was occurrence of MOF with a rapid decrease in AT-III. Therefore, it is conceivable that C1-INH and AT-III function independently in vivo. In this case, it appears possible that activation of plasma kallikrein was elicited by overreacting on the previous night through cholinergic stimulation (45) via the hypothalamoneurohypophyseal axis, resulting in the release of plasminogen (HF)-activating enzyme (19, 20) releasing hormone. This would result in the activation of plasma kallikrein and in concurrent activation of tissue factor pathway of coagulation cascade. Therefore, the initial steps of kallikrein generation and tissue factor pathway activation are inhibited by the action of C1-INH and TFPI, and the final step, thrombin generation, is inhibited by AT-III. As observed in our case 1 during her younger days and in Mineshita's case, acute attacks of HANE can be resolved without specific treatment such as a C1-INH preparation. Thus, the symptoms of acute attack of HANE alter with aging, probably by modulation of biosynthesis of TFPI and/or AT-III. The occurrence of a fulminating thromboembolic lethal end in elderly HANE patients could be regarded as the characteristic course of the disease. Furthermore, the natural history of HANE may be divided into two phases, tentatively termed the "reversible phase" in younger patients and the "irreversible phase" in elderly patients.

Part of this work was supported by a Research Grant for Cardiovascular Disease (SSA-1) from the Ministry of Health and Welfare of Japan. This article is dedicated to the memory of the author's daughter, Hiroko Kogame, her husband, Masaaki Kogame, MD., and their son, Mitsumasa, who were among over 6,000 persons killed by the Hyogo-ken Nanbu Earthquake in 1995, as well as to our patients with HANE who suffered fulminant lethal attacks.

References

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