

Autoantibodies in Angioneurotic Edema

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Introduction

The first case of the acquired form of C1 inhibitor (C1 INH) deficiency was described in 1972 by Caldwell and coworkers (1). A lymphosarcoma patient presented with angioedema attacks identical to that seen in Hereditary Angioedema. The patient serum exhibited low C2, C4, marked reduction in C1 inhibitor activity, and also low function of the C1 macromolecule. In addition, the patient serum contained a 7s IgM paraprotein, and metabolic studies showed hypercatabolism of C1q and C1 INH. The addition of the patient serum to normal human serum depleted the C1 functional activity of the normal serum (1).

Several reports describing similar patients with lymphosarcoma, chronic lymphocytic leukemia, or lymphomas with a 7s or low molecular weight IgM have been documented (2,3). This syndrome, acquired angioedema (AAE type I), is most commonly associated with lymphoproliferative disorders but is also observed alone or in association with other diseases (4). A second form of AAE (type II) was documented in 1986 and was found to be mediated by an IgG autoantibody (5). The autoantibodies are oligoclonal or monoclonal. Recently, Cicardi et al. found that the majority of the paraproteins in AAE type I are frequently circulating autoantibodies to C1 INH usually encountered in AAE type II, suggesting that the distinction between type I and type II AAE may be artificial. The focus of this review is to define the role and the

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specificity of the C1 inhibitor autoantibodies. It is also meant to define some of the possible pathophysiological mechanisms associated with the acquired form of angioneurotic edema.

C1 Inhibitor

Human C1 inhibitor (C1 INH), a serine protease inhibitor with a molecular weight of 105 kDa, is a member of the serpin superfamily. C1 INH is a major inhibitor of the inflammatory response via its inactivation of the C1r and C1s proteases of the complement system, factors XIa and XIIa of the coagulation system, plasmin of the fibrinolytic pathway, and kallikrein of the kinin system (6). Deficiency or dysfunction of C1 INH, results in unregulated activation of the complement and the kinin systems.

C1 INH differs from other protease inhibitors in that it is extremely heavily glycosylated (~50%) for a plasma protein (6). It consists of a single polypeptide chain containing 478 amino acids mainly synthesized by the liver, fibroblasts, monocytes, and megakaryocytes (6). C1 INH inactivates susceptible protease by the same mechanism as the other protease inhibitor of the serpin superfamily. Inactivation of a protease results from covalent binding to a site within the inhibitor that mimics the natural substrate of the protease (7). Susceptible protease reacts with C1 INH to form detergent stable bimolecular complexes (8).

Acquired C1 Inhibitor Deficiency

Characteristics of AAE Patients

The clinical characteristics of AAE patients resemble those with hereditary angioedema (9), in that the patients exhibit low or undetectable CH50, C2, C4, and functional C1, in addition to low levels of C1 INH and typical clinical manifestations of angioedema, such as swellings of varying severity and location. The skin of the extremities, groin, and face is often involved, as is the mucosa of the oro-pharynx where life-threatening laryngeal edema may evolve (10). Edema of the gastrointestinal tract causes nausea, vomiting, abdominal pain, and occasionally diarrhea. Transient aphasia and hemiplegia are serious but less frequent manifestations (11). Attacks usually crescendo over several hours and spontaneously resolve over several days. Exacerbation of attacks has been associated with menstruation, whereas there is a reported decrease in attacks during the last trimester of pregnancy and after menopause (12). CNS symptoms suggestive of focal cerebral edema, such as headaches, hemiparesis, or seizures may also occur. Distinction of intra-abdominal angioedema from an acute surgical abdomen is paramount, but difficult. During attacks, C1 INH functional

activity is reduced; serum C2 and C4 may be normal between attacks but is reduced during attack. Also, there are reductions during attacks in factor XII plasma levels coupled with an increase in kallikrein activity and in plasmin-alpha-2-antiplasmin complexes (13). These serologic findings are all consistent with activation of both the complement classical pathway and the contact system for fibrinolysis and kinin formation. During attacks, patients with AAE also have increased urinary histamine levels (14). However, histamine is not considered to be central in the pathogenesis of the angioedema, because the patients do not experience puritus (13), and antihistamines neither prevent nor ameliorate the angioedema. Kinins, on the other hand, are mole for mole of equal potency to histamine and cause histologic lesions similar to histamine, but without pruritus, making them attractive etiologic molecules for the AAE (15).

Two products generated from complement activation and contact phase system have kinin activity. The more controversial is the degradation product of C2b that has kinin-like activity (16). A more likely candidate molecule in the pathogenesis of AAE is bradykinin, a vasoactive peptide generated by the proteolytic effect of kallikrein on kininogen (17).

Characterization and Epitope Mapping of C1 INH Autoantibodies

The epitope recognized by several autoantibodies has been mapped (18,19). The available data from six autoantibodies suggest that, in the intact C1 INH molecule, there are two potential epitopes that can be recognized by C1 INH autoantibodies located at residues 446–449 and 452–455 of the C1 INH molecule. Different antibodies may recognize one or both of these epitopes (18). C1 INH autoantibodies could be monoclonal or polyclonal, of the IgG, IgM, or IgA isotype (20).

Bindings of the autoantibodies to the C1 INH render the C1 INH molecule susceptible to proteolytic cleavage by an unknown protease (presumably C1s) to a 96-kDa functionally inactive molecule. Indeed, one of the major characteristics of AAE patients is the presence of the 96-kDa C1 INH species in their plasma (21). Interestingly, the autoantibodies react with the 96-kDa C1 INH molecule at a much lower rate compared with the native 105-kDa C1 INH molecule.

Pathogenetic Role of C1 INH Autoantibodies

C1 INH in AAE patients is circulating in the cleaved 96-kDa functionally inactive form. The autoantibodies do not cleave C1 INH directly (22). However, they are most likely to bind the C1 INH close to the active site and interfere with C1 INH function, and convert the C1 INH from an inhibitor to a substrate.

Method of Detection

This current assay used to detect the C1 INH autoantibodies is based on solid-phase ELISA in which a solid-phase is coated with C1 INH and is then incubated with the patient's serum. Immunoglobulins binding to the C1 INH are detected with appropriate enzyme-labeled anti-immunoglobulin IgG (23,24).

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