

The Editors welcome submissions for possible publication in the Letters section. Authors of letters should: • Include no more than 300 words of text, three authors, and five references • Type with double-spacing • Send three copies of the letter, an authors' form (see Table of Contents for location) signed by all authors, and a cover letter describing any conflicts of interest related to the contents of the letter.

Letters commenting on an *Annals* article will be considered if they are received within 6 weeks of the time the article was published. Only some of the letters received can be

published. Published letters are edited and may be shortened; tables and figures are included only selectively. Authors will be notified that the letter has been received. If the letter is selected for publication, the author will be notified about 3 weeks before the publication date. Unpublished letters cannot be returned.

Annals welcomes electronically submitted letters. The Internet address is www.acponline.org/shell-cgi/letter-article.pl.

Acquired C1 Esterase Inhibitor Deficiency

TO THE EDITOR: We disagree with Markovic and colleagues' treatment recommendations for acquired C1 esterase deficiency (1) because they could lead to mistreatment of patients with this illness and life-threatening situations.

The authors draw conclusions from 22 cases with supposed "acquired C1 esterase inhibitor deficiency angioedema" but present only partial results of two cases that have no clearly documented diagnosis. Acute angioedema attacks were treated with antihistamines, corticosteroids, or epinephrine. Symptom resolution was attributed to this therapy, but the cause-and-effect relationship was not clearly demonstrated (the attacks could have resolved spontaneously). Moreover, the authors did not document these treatments with published references. They also stated that C1 inhibitor is indicated only for a limited number of patients with the hereditary form of the disease, and they cite only two old and not representative references.

Nevertheless, the first-line treatment of acute attacks of angioedema should be intravenous C1 inhibitor concentrate (where available), although the acquired form of the disease may require higher doses (2–5). Long-term prophylaxis can be achieved with attenuated androgens or, preferably, antifibrinolytic drugs and, in some cases, C1 inhibitor infusions (2–5). Finally, we cannot forget the treatment of the underlying disease (3–5). The available evidence indicates that angioedema due to C1 esterase deficiency does not respond to adrenaline, corticosteroids, or antihistamines.

In the diagnostic work-up flow sheet in Markovic and colleagues' review, the main screening measures should be C4 levels and C1 inhibitor function (3–5). C1q is not a screening measure, but it provides complementary data that permit discerning between acquired and hereditary forms of C1 esterase deficiency. Moreover, "C1 antigen" in the flow sheet should be "C1 inhibitor antigen." Finally, the review did not cite some important series of acquired angioedema (5).

Teresa Caballero, MD, PhD

Maria Concepcion Lopez-Serrano, MD, PhD

Margarita Lopez-Trascasa, PhD

Hospital Universitario La Paz

28046 Madrid, Spain

References

1. Markovic SN, Inwards DJ, Frigas EA, Phylilly RP. Acquired C1 esterase inhibitor deficiency. *Ann Intern Med.* 2000;132:144-50.

2. Waytes AT, Rosen FS, Frank MM. Treatment of hereditary angioedema with a vapor-heated C1 inhibitor concentrate. *N Engl J Med.* 1996;334:1630-4.

3. Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore).* 1992;71:206-15.

4. Carreer FM. The C1 inhibitor deficiency. A review. *Eur J Clin Chem Clin Biochem.* 1992;30:793-807.

5. Cicardi M, Bergamaschini L, Cugno M, Beretta A, Zingale LC, Colombo M, et al. Pathogenetic and clinical aspects of C1 inhibitor deficiency. *Immunobiology.* 1998;199:366-76.

TO THE EDITOR: Markovic and colleagues have written an excellent review on angioedema due to acquired C1 esterase inhibitor deficiency (1). However, from a practical standpoint, their proposal for diagnostic work-up in patients with angioedema of unknown cause is of concern: It is time-consuming and expensive to test three complement proteins before determinations of C1 esterase inhibitor activity in patients with suspected angioedema. In addition, C3 and C4 levels may be within normal limits during symptom-free intervals. Therefore, if the algorithm provided is used, some patients may be misdiagnosed. It seems more feasible to first determine C1 esterase inhibitor activity, which may detect nearly all types of C1 esterase inhibitor deficiency, as stated by Markovic and colleagues. If activity is within normal limits, no further laboratory tests are necessary. If activity is low (<70%), quantitative determination of C1 esterase inhibitor protein and C1q will establish the correct diagnosis. This work-up is more convenient to both patient and physician, especially in the outpatient setting. Laboratory costs and time to diagnosis will be reduced by nearly 50% compared to the approach outlined by Markovic and colleagues. Medical practice should always be guided by pathophysiologic considerations but must also rely on quick and proper diagnostic work-up. Academic approaches should not delay diagnosis or therapy.

Thomas Grünewald, MD

Klinikum "St. Georg" Leipzig

D-04129 Leipzig, Germany

Reference

1. Markovic SN, Inwards DJ, Frigas EA, Phylilly RP. Acquired C1 esterase inhibitor deficiency. *Ann Intern Med.* 2000;132:144-50.

TO THE EDITOR: Markovic and colleagues' review (1) contains many unsupported statements that may promote inappropriate therapy. The authors' statements that corticosteroids, epinephrine, heparin, and antihistamines are effective therapy for acquired angio-

edema are misleading. No convincing published evidence suggests that any of these agents is effective therapy for either form of the disease. If the retrospective analysis of the patients treated at the Mayo Clinic indicates efficacy of these agents, these data should have been presented. In addition, both replacement therapy with C1 inhibitor concentrate and prophylaxis with androgen derivatives are frequently ineffective or marginally effective in acquired C1 inhibitor deficiency. This effect is probably secondary to anti-C1 inhibitor autoantibodies that interfere with C1 inhibitor function. The authors' description of the pathogenesis of angioedema ignores published evidence that the contact system mediates angioedema. As the authors summarize, the roles of C2 kinin and bradykinin have been debated for many years (2). Recent data confirmed findings from previous studies that indicated a major role for bradykinin. Contrary to the authors' comments, angiotensin-converting enzyme inhibitors clearly induce angioedema in patients with C1 inhibitor deficiency. This is consistent with bradykinin inactivation by angiotensin-converting enzyme. Markovic and colleagues also state that "all available published articles were reviewed and included in the manuscript." The reference list, however, included only a small portion of the published literature on the subject and excludes at least two previous patient series. Finally, specific data were reported for only 2 of 22 patients reviewed. Information on the remainder of the patients is presented only in the form of conclusions, without reference to the data. The reader, therefore, cannot make an independent judgment of the information discussed.

Marco Cicardi, MD
Angelo Agostoni, MD
University of Milan
Milan, Italy

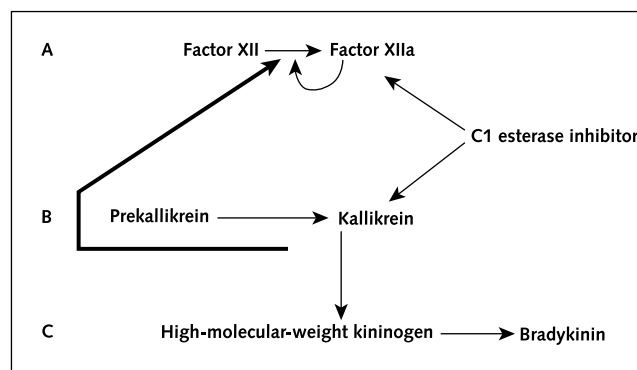
Alvin E. Davis III, MD
Center for Blood Research
Boston, MA 02115

References

1. Markovic SN, Inwards DJ, Frigas EA, Phyllyk RP. Acquired C1 esterase inhibitor deficiency. *Ann Intern Med.* 2000;132:144-50.
2. Cicardi M, Bergamaschini L, Cugno M, Beretta A, Zingale LC, Colombo M, et al. Pathogenetic and clinical aspects of C1 inhibitor deficiency. *Immunobiology.* 1998;199:366-76.

TO THE EDITOR: The review on acquired C1 esterase inhibitor deficiency (1) reports that C2 kinin is the cause of the swelling. This peptide was originally described as a plasmin-cleavage product of C2b, and a synthetic peptide appears to possess such activity (2). However, it has not been possible to activate human plasma that is deficient in C1 inhibitor to yield a kinin other than bradykinin (3, 4), and bradykinin levels are elevated in plasma of patients with hereditary angioedema during attacks of swelling. Furthermore, swelling has never occurred in members of one unique family with a dysfunctional C1 inhibitor protein that is defective in inhibiting complement but is normal in inactivating plasma kallikrein and fac-

Figure. Pathway for bradykinin formation and function of C1 esterase inhibitor on factor XIIa and kallikrein.



A. Activation of factor XII by autodigestion and kallikrein feedback. B. Conversion of prekallikrein to kallikrein. C. Digestion of kininogen to release bradykinin.

tor XIIa (5). These data all suggest that bradykinin is the key mediator of swelling in C1 inhibitor deficiency (whether hereditary or acquired) and that C1 inhibitor has a role as an inhibitor of bradykinin formation (Figure). Although inhibitors of plasmin or plasminogen activation, such as ϵ -amino caproic acid, provide effective treatment of C1 inhibitor deficiency, the mechanism by which this occurs and the role of plasmin in the process are not yet clear.

Allen P. Kaplan, MD
Medical University of South Carolina
Charleston, SC 29425

References

1. Markovic SN, Inwards DJ, Frigas EA, Phyllyk RP. Acquired C1 esterase inhibitor deficiency. *Ann Intern Med.* 2000;132:144-50.
2. Strang CJ, Cholin S, Spragg J, Davis AE III, Schneeberger E, Donaldson VH, et al. Angioedema induced by a peptide derived from complement component C2. *J Exp Med.* 1988;168:1685-98.
3. Fields T, Ghebrehiwet B, Kaplan AP. Kinin formation in hereditary angioedema plasma: evidence against kinin derivation from C2 and in support of "spontaneous" formation of bradykinin. *J Allergy Clin Immunol.* 1983;72:54-60.
4. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-oedema. *Lancet.* 1998;351:1693-7.
5. Zahedi R, Wisniewski J, Davis AE III. Role of the P2 residue of complement 1 inhibitor (Ala⁴⁴³) in determination of target protease specificity. Inhibition of complement and contact system proteases. *J Immunol.* 1997;159:983-8.

TO THE EDITOR: Markovic and colleagues (1) reviewed the clinical and laboratory features and management of acquired C1 esterase inhibitor deficiency. Although most cases of acquired angioedema have been associated with lymphoproliferative disorders or autoantibodies directed at the inhibitor protein causing the functional deficiency (the autoimmune form of the disease) (2), increasing evidence suggests that infections may also contribute to the development of acquired angioedema.

Markovic and colleagues, however, did not mention a report on two women with acquired angioedema caused by C1 esterase inhibitor deficiency who were found to have hepatitis C virus infection and who developed chronic hepatitis (3). The putative association between chronic hepatitis C and liver disease and the acquired form of angioedema was further supported by the fact that during and after an attack of severe angioedema, one of these two patients had a “flare-up” in aminotransferase activities. The patients were evaluated for autoantibodies to C1 esterase inhibitor protein. Of interest, their sera did not recognize the target protein (3).

Recently, we found a high prevalence (12%) of autoantibodies to C1 esterase inhibitor in patients who had liver cirrhosis caused by chronic hepatitis B or C virus infection or by alcohol abuse but who did not have a history of angioedema, autoimmune disease, or lymphoproliferative disease. Patients with autoantibodies had significantly decreased serum C1 esterase inhibitor levels compared with patients without autoantibodies ($P = 0.016$; Wilcoxon signed-rank test). The decrease in C1 esterase inhibitor protein levels, however, did not cause clinical symptoms of angioedema (unpublished data).

It is tempting to hypothesize that chronic infections, including chronic hepatitis B and C, might initiate an autoimmune response manifested by generation of autoantibodies to the inhibitor protein in genetically susceptible persons. Whether autoantibodies to the inhibitor protein or the increased consumption and impaired synthesis of the protein in the cirrhotic liver are the key factor remains to be elucidated.

Antal Csepregi, MD

Elemér Nemesánszky, MD, PhD

Polyclinic of the Hospitaller Brothers of St. John of God in Budapest
Budapest, Hungary

References

1. Markovic SN, Inwards DJ, Frigas EA, Phyllyk RP. Acquired C1 esterase inhibitor deficiency. *Ann Intern Med.* 2000;132:144-50.
2. Cicardi M, Beretta A, Colombo M, Gioffré D, Cugno M, Agostoni A. Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantibodies in acquired angio-oedema. *Clin Exp Immunol.* 1996;106:475-80.
3. Farkas H, Csepregi A, Nemesánszky E, Pár A, Gyenyey L, Varga L, et al. Acquired angioedema associated with chronic hepatitis C. *J Allergy Clin Immunol.* 1999;103:711-2.

IN RESPONSE: Caballero and colleagues take issue with the two cases illustrating acquired C1 esterase deficiency and suggest the need for greater detail in the description of these cases. They also appear to have anticipated a full description of all 22 cases identified in our database. We appreciate the comments, but we felt that a detailed

presentation of all 22 cases would have been inappropriate for the format of our manuscript. The two presented cases were intended to illustrate the typical course of acquired C1 esterase inhibitor deficiency. Caballero and colleagues favor the use of intravenous C1 inhibitor concentrate “where available.” Given the unavailability of this agent in general practice (at least in the United States) and the efficacy of other therapies, we believe that the described management of acquired C1 esterase inhibitor deficiency, successfully used in our institution, is a reasonable approach. Concerning our diagnostic work-up flow chart, we favor screening with commonly available tests, leaving more sophisticated and more expensive testing for confirmation of diagnosis. Therefore, we usually elect not to measure the C1 esterase inhibitor function when screening for this disorder. Cicardi and coworkers comment on the lack of convincing evidence that the agents used in our practice to control symptoms of acquired C1 esterase inhibitor deficiency are effective. Part of the goal of our review was to share our clinical experience with the use of these agents in the successful management of acquired C1 esterase inhibitor deficiency. In our experience, androgen derivatives are effective in the management of acquired C1 esterase deficiency.

The role of bradykinins (as mentioned by Kaplan and Cicardi and colleagues) as mediators of angioedema in this disorder has been debated for years. Some data support the role of both bradykinin and C2 kinin. Although we did not intend to elaborate on this debate, we accept Dr. Kaplan’s suggestions and should have commented on the role of bradykinins as possible mediators of angioedema in acquired C1 esterase inhibitor deficiency.

Csepregi and Nemesánszky comment on the recently published description of two patients who developed acquired C1 esterase inhibitor deficiency in the setting of hepatitis C. Unfortunately, this reference was not available at the time of submission of our manuscript.

Svetomir N. Markovic, MD, PhD

David J. Inwards, MD

Robert P. Phyllyk, MD

Mayo Clinic

Rochester, MN 55905

Correction: Propranolol and Thyroid Storm

In a letter to the editor on propranolol and thyroid storm (1), the dobutamine dose given should be 12 $\mu\text{g}/\text{kg}$ of body weight per minute, not 12 g/kg of body weight.

Reference

1. Ashikaga H, Abreu R, Schneider RF. Propranolol administration in a patient with thyroid storm [Letter]. *Ann Intern Med.* 2000;132:681-2.