

Hereditary angioedema: A half century of progress

Michael M. Frank, MD *Durham, NC*

Keyword: Hereditary angioedema

Abbreviation used

FFP: Fresh frozen plasma

This issue of the Journal contains the proceedings of the Third European C1 Inhibitor Workshop¹ and a Canadian consensus conference review.² They review the findings made in multiple centers over the past decade. In particular, there are excellent reviews of the enormous advances in the nature of the defects in the C1 inhibitor gene that lead to hereditary angioedema, reviews of our current understanding of pathophysiology, and reviews of our colleagues' experience with the clinical syndrome and its treatment. The Journal has recently reviewed laboratory tests used in the evaluation and treatment of patients with hereditary angioedema, as well as the tests used to evaluate complement function in all of the diseases that we are called upon to diagnose and treat.³

There is currently widespread recognition in the allergy community of hereditary angioedema as a clinical entity. It is known to cause episodic nonpitting edema that usually involves the extremities but may affect any external body surfaces, including the genitalia. Patients often have severe abdominal pain due to mucosal swelling in the gastrointestinal tract. The disease can be lethal when angioedema attacks affect the airway.⁴

The progress made in our understanding of this disease over the last 50 years is astonishing. In 1962, before any of the complement defects were known, Landerman et al⁵ suggested that the disease might be due to dysregulation of the kinin system. Our current understanding of pathophysiology has come full circle. Dr Davis reviews data suggesting that uncontrolled bradykinin generation is responsible for angioedema attacks and reviews his

group's elegant studies with the C1 inhibitor knockout mice.⁶ In 1963, Donaldson and Evans⁷ showed that patients with hereditary angioedema had low levels of a plasma protein, C1 inhibitor. This protein was rapidly shown to inhibit elements of the complement-generating, kinin-generating, clotting, and fibrinolytic systems in blood. Patients with hereditary angioedema were shown to be heterozygotes; no homozygous deficient patient with absent C1 inhibitor has ever been described. A wide variety of deletions, translocations, stop codons, and point mutations of the gene that lead to disease have been identified and are discussed.

It is interesting to note that in 1960, long before all of this knowledge was available, Spaulding⁸ had empirically treated members of 1 family with methyltestosterone and noted improvement. Because his explanation of the drug effect was that the methyltestosterone thickened collagen fibers and prevented swelling and because this seemed improbable, the clinical findings were never further explored, and hormonal treatment was not introduced into therapy for more than a decade. We now know that many of the methylated testosterone derivatives provide effective prophylactic therapy. It was shown that treatment with attenuated androgens such as danazol leads to increased levels of C1 inhibitor and a tendency for complement levels to return toward normal.⁹ Our original decision to study danazol was not based on knowledge of the earlier work of Spaulding. We had noted that patients with hereditary angioedema who were taking high-estrogen birth control pills often become more severely ill and that sometimes therapy could be limited to simply stopping birth control pills. Our first attempt at hormonal treatment, although never published, was a double-blind study of high-dose progesterone therapy.^{4,10} Our reasoning was that hereditary angioedema is often much less severe in the later stages of pregnancy and after delivery often becomes more severe. Progesterone increases in the later stages of pregnancy and decreases at the time of delivery. It is interesting that a question concerning progesterone therapy re-emerges in this issue 25 years later. In a double-blind clinical trial of medroxyprogesterone acetate

From the Departments of Pediatrics and Immunology and Medicine, Children's Health Center, Duke University Medical Center.

Received for publication June 14, 2004; revised June 21, 2004; accepted for publication June 22, 2004.

Available online August 9, 2004.

Reprint requests: Michael M. Frank, MD, Department of Pediatrics, Duke University Medical Center, Box 3556, Durham, NC 27710. E-mail: frank007@mc.duke.edu.

J Allergy Clin Immunol 2004;114:626-8.
0091-6749/\$30.00

© 2004 American Academy of Allergy, Asthma and Immunology
doi:10.1016/j.jaci.2004.06.035

(Provera) in a group of white North American women, we found no statistically significant effect on attack frequency, although the patients all reported that they felt better on progesterone therapy. We then went on to study danazol, which had not yet appeared on the market, and the markedly effective response led us to not publish our experience with provera.

These agents do not terminate an ongoing attack. It is believed, but is still controversial, that the drugs cause increased synthesis of the normal protein by the liver in these patients who have 1 normal gene.^{10,11} As such, this is one of the few genetically caused diseases that can be treated effectively with therapy that corrects the biochemical deficiency.

The article by Bowen et al² provides much information on the European and Canadian approach to the treatment of hereditary angioedema. It points out that the United States has fallen behind many nations in caring for these patients. In most centers, danazol or related drugs provide the mainstay of therapy, as they do here in the United States. In Europe, C1 inhibitor, purified from blood plasma, became available decades ago, after our initial article suggesting that the disease could be cured with intravenous C1 inhibitor therapy.¹² Although the experience with C1 inhibitor infusion in all centers, as reported in this issue, is positive, unfortunately, purified C1 inhibitor is still not available in America for the treatment of life-threatening attacks.

We reported in a double-blind study that ϵ -aminocaproic acid provides effective therapy for this disease.¹³ Tranexamic acid, a more powerful analog, is used for therapy in many European nations, but this drug is not available in this country. ϵ -Aminocaproic acid does provide effective therapy, but its use is accompanied by a large number of complications, including, prominently, muscle pain and extreme fatigue. Usually it takes many months of treatment for this lysine analog to produce this highly undesirable side effect, and fortunately, in almost all cases the signs clear when the drug is stopped.

There are some other striking differences between therapy in Europe and America. We do not treat to correct C1 inhibitor or C4 levels, as is recommended in one of the European studies. As we reported⁴ in 1976 and as is confirmed in these reviews, there is no relationship between C1 inhibitor levels and disease severity; we try to find the lowest dose of drug that will relieve clinical symptoms, paying no attention to C1 inhibitor or C4 levels. Epinephrine is not mentioned as part of the European armamentarium, but I always use it, because my impression is that some patients do respond, albeit poorly. The use of fresh frozen plasma (FFP) is advocated in some articles. We never use FFP because several of those who have taken care of many patients have seen patients get worse on FFP as more substrate for edema formation is provided. It is true that usually FFP terminates attacks. Danazol is advocated in children in one report. Because of the danger of early epiphyseal closure, we do not use it in children, but in truth, I have no experience in this area. Finally, the use of methyltestosterone in males is not

mentioned. In Europe, many patients' medical bills are paid by the state, but here, where the cost of medication is an issue, methyltestosterone, because it is inexpensive and usually effective, should be considered for therapy in men.

The positive experience with C1 inhibitor treatment in Europe and the successful use of this agent in small trials in this country led to the hope that C1 inhibitor would become available in the United States. A double-blind clinical trial was performed that used C1 inhibitor to terminate attacks of hereditary angioedema. However, certainly in retrospect, the trial design was seriously flawed and did not lead to a statistically significant difference between C1 inhibitor and placebo. The production of the C1 inhibitor used in that study as a pharmaceutical was discontinued. However, as a result of this unsuccessful study and because of the concerted action of well-organized, well-motivated, and intelligent patient-support groups, there has been renewed interest in making agents available for treatment. Multiple pharmaceutical companies are in the process of developing drugs that, it is hoped, will be useful in this disease. Such drugs are needed for patients who cannot tolerate androgens, for children, for pregnant women, and for patients who respond poorly to androgen therapy. Moreover, none of the drugs currently available in this country reliably terminates attacks.

The range of new drugs in development is impressive and is discussed in this issue. Studies are now planned for the use of the C1 inhibitor preparation purified from plasma that has been available in Europe for 2 decades. C1 inhibitor produced by recombinant technology is being developed for clinical use. A kallikrein antagonist is currently undergoing clinical trial, and evaluation of a bradykinin receptor 2 antagonist is planned. The therapeutic possibilities in the near future for patients with hereditary angioedema seem quite optimistic.

A number of hereditary angioedema-like clinical syndromes have been defined and are discussed in the issue, as well as in a recent review by Wen et al.³ These include acquired C1 inhibitor deficiency, which can be a result of malignancy, autoantibody to C1 inhibitor, or autoimmune states that consume C1 inhibitor.^{14,15} A fascinating syndrome has been noted on both sides of the Atlantic that has been called type III hereditary angioedema.^{16,17} Although the pathophysiology of this syndrome is not clear, clinically it closely resembles hereditary angioedema; however, it occurs only in women. In some studies it is linked to estrogen treatment. In other studies it has affected some women without estrogen treatment. C1 inhibitor and complement function are reported as normal, and the pathophysiology is still unknown, but the striking clinical similarity between this syndrome and C1 inhibitor deficiency suggests that further study of the pathophysiology of this syndrome will provide important insights into the bases of angioedema.

Thus, in approximately 45 years, we have gone from minimal understanding of cause, pathophysiology, and treatment of this disease to an extensive understanding of many of these issues. Not discussed in this issue is the fact

that C1 INH inhibitor has powerful anti-inflammatory activity and is being studied as a therapeutic agent in a wide variety of settings, such as patients undergoing cardiopulmonary bypass or transplantation and those with myocardial infarcts and inflammatory states.¹⁸ These states are associated with complement or kinin system activation, and C1 inhibitor is presumably acting to downregulate this activation. Thus far, most—but not all—of the anti-inflammatory studies listed previously have been performed in animals, but we can expect extension to the clinic soon.

REFERENCES

1. Agostoni A, Zingale L, Williams K, Cicardi M, Williams K, Farkas H, et al. Hereditary and acquired angioedema: problems and progress. Proceedings of the Third European C1-Esterase Inhibitor Deficiency Workshop and Beyond. *J Allergy Clin Immunol*. In press 2004.
2. Bowen T, Cicardi M, Farkas H, Bork K, Kreuz W, Zingale L, et al. Canadian 2003 International Consensus Algorithm for the diagnosis, therapy and management of hereditary angioedema. *J Allergy Clin Immunol* 2004;114:629-37.
3. Wen L, Atkinson JP, Giclas P. Clinical and laboratory evaluation of complement deficiency. *J Allergy Clin Immunol* 2004;113:585-93.
4. Frank MM, Gelfand JA, Atkinson JP. Hereditary angioedema: the clinical syndrome and its management. *Ann Intern Med* 1976;84:589-93.
5. Landerman NS, Webster ME, Becker EL, Ratcliffe HE. Hereditary angioneurotic edema. *J Allergy* 1962;33:330-41.
6. Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. *J Clin Invest* 2002;109:1057-63.
7. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema. *Am J Med* 1963;35:37-44.
8. Spaulding WB. Methyltestosterone therapy for hereditary episodic edema (hereditary angioneurotic edema). *Ann Intern Med* 1960;53:739-45.
9. Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol. *N Engl J Med* 1976;295:1444-8.
10. Frank MM. Effect of sex hormones on the complement-related clinical disorder of hereditary angioedema. *Arthritis Rheum* 1979;22:1295-9.
11. Pappalardo E, Zingale LC, Cicardi M. Increased expression of C1 inhibitor mRNA in patients with hereditary angioedema treated with danazol. *Immunol Lett* 2003;86:271-6.
12. Gadek JE, Hosea SW, Gelfand JA, Santaella M, Wickerhauser M, Triantaphyllopoulos DC, et al. Replacement therapy in hereditary angioedema. *N Engl J Med* 1980;302:542-6.
13. Frank MM, Sergeant JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema. A double-blind study. *N Engl J Med* 1972;286:808-12.
14. Alsenz J, Lambris JD, Bork K, Loos M. Acquired C1 inhibitor (C1-INH) deficiency type II: replacement therapy with C1 INH and analysis of patients' C1-INH and anti-C1-INH autoantibodies. *J Clin Invest* 1989;83:1794-9.
15. Cicardi M, Zingale LC, Pappalardo E, Folcioni A, Agostoni A. Autoantibodies and lymphoproliferative diseases in acquired C1 inhibitor deficiencies. *Medicine (Baltimore)* 2003;82:274-81.
16. Binkley KE, Davis A III. Clinical, biochemical and genetic characterization of a novel estrogen dependent inherited form of angioedema. *J Allergy Clin Immunol* 2000;106:546-50.
17. Bork K, Barnstedt S-E, Koch P, Traupe H. Hereditary angioedema with normal C1 inhibitor activity in women. *Lancet* 2000;356:213-7.
18. Caliezi C, Willemin WA, Zoerleder S, Redondo M, Eisele B, Hack CE. C1 esterase inhibitor: an anti-inflammatory agent and its potential use in the treatment of diseases other than hereditary angioedema. *Pharmacol Rev* 2000;52:91-112.