

Refractory exacerbations of hereditary angioedema with associated *Helicobacter pylori* infection

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Hereditary angioedema (HAE), an autosomal dominant disorder, is characterized by the defective production of C1 inhibitor by 1 of the 2 genes present on chromosome 11. The inhibitory defect may be characterized by low antigenic or functional levels of C1 inhibitor.^{1,2} The first component of the complement system, C1, is a pentamolecular calcium-dependent complex consisting of 1 C1q, 2 C1r, and 2 C1s molecules. C1 inhibitor combines with activated C1r and C1s to inhibit complement activation. The hallmark of relapses of HAE is low levels of C4 and C2, with normal levels of C1 and C3. Clinical manifestations are recurrent attacks of subcutaneous edema typically involving the face, neck, and extremities. In addition to soft tissue swelling, other symptoms include dyspnea caused by upper airway obstruction and abdominal pain caused by mesenteric edema. Triggers for exacerbations include trauma, surgery, and emotional stress. There are reports of therapy with angiotensin-converting enzyme inhibitors causing worsening of edema and even death.³ Although infection has been implicated as a cause of urticaria, the role of infection in exacerbations of angioedema has not been documented.

We report a 42-year-old Latin American male with recurrent episodes of edema since the age of 7 years. He has had swelling of his extremities, lips, ears, eyes, hands, and feet, as well as his penis and scrotum. He has been intubated 3 times because of respiratory compromise secondary to edema of the tongue and throat. A diagnosis of HAE was entertained in February 1995 on the basis of low C1 inhibitor and C4 with normal C1 (Table I).

The patient had exacerbations of his symptoms with trauma. In addition, he has had epigastric pain, attributed to HAE, and was never evaluated by endoscopy. He was treated with attenuated androgens (stanozolol) and ranitidine. Despite therapy with stanozolol up to 36 mg daily, he had exacerbations of symptoms requiring recurrent hospitalizations. Typically, he was treated with aminocaproic

Abbreviation used

HAE: Hereditary angioedema

acid, fresh frozen plasma, and corticosteroids. Stanozolol was stopped, and danazol was started at a dose of 200 mg given three times daily in March 1996, which was tapered as he improved. His liver enzymes were monitored periodically and were mildly elevated.

His symptoms were stable while receiving danazol 200 mg twice daily until March 1997 when he developed abdominal pain, vomiting, and swelling of his face. He was hospitalized for observation and given intravenous aminocaproic acid and fresh frozen plasma. He was discharged on a regimen of danazol 200 mg three times daily. He was readmitted twice with similar manifestations in April 1997. Danazol was increased to 200 mg four times daily. Despite maximum therapy, he again experienced vomiting and facial swelling and required short-stay hospitalization. C3 remained normal but C4 and C1 inhibitors were low (Table I).

During all these episodes, he had persistent abdominal pain localized in the epigastrium and associated with heartburn. Epigastric pain was usually relieved after vomiting. H2 blockers were ineffective. The results of physical examination were positive for point tenderness in the epigastrium. Endoscopy was performed in June 1997 and showed mild chronic active gastritis. Biopsy specimens were positive for *Helicobacter pylori*. C3 and C4 levels were essentially unchanged. Triple therapy for *H pylori* was started (bismuth subsalicylate 530 mg four times daily, metronidazole 250 mg three times daily, and amoxicillin 500 mg four times daily for 14 days).

Subsequently epigastric symptoms improved drastically, and he has had no further exacerbations of angioedema. Danazol was tapered from 800 mg to 400 mg per day. C4 levels returned to normal. The breath urea test response as follow-up for *H pylori* infection was negative.

Several recent reports have suggested an association between *H pylori* infections and chronic urticaria.⁴⁻⁵ However, the mechanism has not been explained. Bohmeyer et al⁴ observed that successful treatment of *H pylori* gastritis was associated with resolution of chronic urticaria; however, this correlation has not been universal.⁵ This is the first report of a chronic infection, namely *H pylori*, related to recurrent attacks of HAE despite

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TABLE I. Serial follow-up studies of serum C3, C4, and C1 inhibitor

	Feb 95	Nov 95	Apr 96	Aug 96	Mar 97*	Jun 97†	Nov 97‡
C3 (N: 86- 104 mg/dL)	134	154	98	100	102	105	151
C4 (N: 20- 59 mg/dL)	13	9	20	12	<8	<8	53.8
C1 inhibitor func (% of normal)	32	5	65	70	15	4	41

N, Normal range; C1 inhibitor func, functional level of C1-esterase inhibitor.

*Start of exacerbations of HAE.

†Start of therapy for *H pylori*.

‡Follow-up studies showed improvement in all parameters.

high doses of attenuated androgens. The most likely explanation might be the activation of the classical pathway of complement system by antigen-antibody complexes. Antibodies could bind to bacterial antigens with further activation of C1. This would result in further

depletion of C1 inhibitor and unchecked activation of subsequent complement components.

We conclude that *H pylori* infection may be an important factor in refractory exacerbations of HAE. Because this is such a common infection of the gastrointestinal tract, it might be an important reason for refractory HAE. Furthermore, it should be emphasized that the recurrent abdominal pain common in patients with HAE might be caused by gastritis or peptic ulcer disease associated with *H pylori* infection. In addition, this infection should be treated appropriately.

REFERENCES

1. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioedema: absence of serum inhibitor of C1-esterase. *Am J Med* 1963;35:37-44.
2. Sim TC, Grant JA. Hereditary angioedema: its diagnostic and management perspectives. *Am J Med* 1990;88:656-64.
3. Adkinson D, Sim TC, Lee J, Grant JA. Hereditary angioedema exacerbated by angiotensin converting enzyme inhibitor. *J Allergy Clin Immunol* 1993;91:364.
4. Bohmeyer J, Heller A, Hartig C, Wetenberger-Treumann M, Huchzermeyer H, Otte HG, et al. Association of chronic urticaria with *Helicobacter pylori*-induced antrum gastritis. *Hautarzt* 1996;47:106-8.
5. Wedi B, Wagner S, Werfel T, Manns MP, Kapp A. Prevalence of *Helicobacter pylori*-associated gastritis in chronic urticaria. *Int Arch Allergy Immunol* 1998;116:288-94.