



Understanding **Hereditary Angioedema**

By Ronale Tucker Rhodes, MS

HAE is a life-threatening disease that is difficult to diagnose, and only recently has medication been approved by the FDA to treat it. Yet, even with these new treatments, the disease continues to plague patients, so learning how to live with the condition is imperative.

The blog is titled “Di Has Stories... (and they’re all true).” Diana won’t reveal her last name because she doesn’t want her “students finding me like they did on Facebook.” But she does provide some details about herself. She’s 35, and she’s spent the last “15 years being beaten down by a disease” that has caused her to be “too sick.” According to Diana, she has been too sick to go out with friends, too sick to wear certain clothes and shoes, too sick to make plans for the future in case she has to cancel them, too sick to travel, too sick to get in shape, too sick to take up hobbies, and in 2008, she

became too sick to work. After nine years of living with a mysterious illness, she was diagnosed at the age of 29 with hereditary angioedema (HAE).

What Is HAE?

HAE, a rare and potentially life-threatening genetic condition that occurs in approximately one in 10,000 to one in 50,000 people in the U.S.,¹ is an immune-mediated disease that is often treated by immunologists. HAE is caused by an autosomal dominant disorder of C1 inhibitor (C1-INH) deficiency. There are three types of HAE. Type I HAE occurs when there are low plasma levels of a normal C1-INH protein. Type II HAE occurs when there are normal or elevated levels of a dysfunctional C1-INH. Men and women are equally affected with HAE types I and II. Type III HAE has been recently identified as an estrogen-dependent inherited form of angioedema occurring mainly in women with normal functional and quantitative levels of C1-INH.² Diana has type III HAE.

Typically, HAE is hereditary because the genetic defect is passed on in families, which is why the disease is so named. If one of a child's parents has HAE, the child has a 50 percent chance of inheriting it. However, 20 percent of HAE cases are not hereditary. Instead, they are a result of a spontaneous mutation of the C1-INH gene at conception. Diana's HAE is not hereditary. According to Diana, she is a "mutant, meaning that I have no family history of HAE ... [but] I am not as alone as I thought I was."

Diagnosing HAE

It is common for those with HAE to remain undiagnosed for years. Symptoms of HAE include episodes of edema (swelling) in various body parts, including the hands, feet, face and airway — all of which are both disfiguring and disabling. In addition, patients often have bouts of excruciating abdominal pain, nausea and vomiting that are caused by swelling in the intestinal wall. Unfortunately, frequent and severe abdominal pain is often inappropriately diagnosed. Oftentimes, patients undergo unnecessary exploratory surgery, and in many cases, physicians diagnose abdominal pain as psychosomatic.¹ Undiagnosed HAE also has been known to result in narcotic dependence.²

For type I HAE and type II HAE patients, symptoms usually become apparent in the first or second decade of life. Approximately 40 percent of people with HAE experience their first episode before age 5, and 75 percent before age 15. Type III HAE, however, is not found until the

second decade of life or later and occurs only rarely before puberty.²

There are some clinical characteristics that should lead a physician to suspect HAE. These include attacks that may be preceded or accompanied by a nonpruritic, flat, erythematous mottling (redness of the skin where swelling occurs) or erythema marginatum (pink rings on the trunk and inner surfaces of the arms and legs); prolonged attacks that increase over the first 24 hours and then slowly subside over the next 48 to 72 hours before full resolution; periods when swelling does not occur for several weeks or more after an attack; and failure of attacks to respond to treatment with epinephrine, antihistamines or corticosteroids.³

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However, clinical characteristics of HAE must be confirmed by laboratory tests that will confirm a C1-INH deficiency. According to Professor of Medicine Bruce L. Zuraw, a physician/researcher at the University of California at San Diego, patients should be initially screened by measuring complement C4 antigenic levels, which are typically low even when patients are not swelling and, in most cases, low during a swelling attack. If the C4 level is decreased, or if the level is normal but all of the clinical characteristics are met, C1-INH antigenic and functional levels should be tested. And, because the test for C1-INH function used in the U.S. is insensitive and may be inaccurate, it is recommended to repeat the C4 and C1-INH functional levels during an HAE attack. In addition, patients who have no family history of HAE and report onset of symptoms in the fourth decade of life should be screened for acquired angioedema by testing the C1q component.³

Patients needing assistance with an HAE diagnosis can get help locating doctors in their area who treat HAE patients. This list is available from the U.S. Hereditary Angioedema Association (HAEA) by contacting Michelle Williamson, director of patient services and clinical programs, at michellewilliamson@haea.org or (972) 814-5205.⁴

Treating HAE

Prior to 2008, HAE patients were prescribed anabolic steroids to treat HAE. But, while they were shown to be useful, they were not well-tolerated by many women, and they were directly linked to liver toxicity and caused an increase in cholesterol levels. Plus, they were unable to be used to treat children.⁵

Then, in late 2008, Cinryze, a C1-inhibitor for preventing HAE attacks in teenagers and adults, was approved by the FDA. Manufactured by ViroPharma Inc., Cinryze is administered intravenously and is approved for home infusion. In late 2009, the FDA approved Berinert to treat acute facial and abdominal attacks in HAE patients. Manufactured by CSL Behring, it also is delivered intravenously. Shortly thereafter in 2009, the FDA approved Kalbitor to treat sudden and potentially life-threatening fluid buildup that can occur in patients 16 years and older with HAE. Kalbitor is manufactured by Dyax Corp., and

unlike the other two drugs, it is administered through subcutaneous injections.⁵

There also are two other HAE therapies that are under investigation. Firazyr, manufactured by Shire HGT, is an acute attack therapy that is administered subcutaneously and is already approved in Europe. Shire filed a complete response to the FDA in February based on positive results from its FAST-3 study and an ongoing self-administration study, as well as the previously published

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FAST-1 and FAST-2 studies. Rhucin, from Pharming Group NV, is a recombinant human C1 inhibitor protein that is derived from the milk of genetically altered rabbits. Pharming is in the process of applying for a U.S. license for Rhucin.⁵

There are some medicines that HAE patients must avoid, including ACE inhibitors and estrogen-derived medications (birth control pills and hormone replace-

Social Networking Sites for HAE Patients and Their Families

- **All About HAE** (www.allabouthae.com/consumer)

All About HAE is a community for patients and family members with HAE that provides resources and tools to manage and treat an HAE attack.

- **Canadian Hereditary Angioedema Network [CHAEN]** (www.haecanada.com/m.php?p=ehome)

CHAEN is dedicated to increasing awareness of issues affecting care and treatment of HAE patients, encouraging peer support and information sharing, and encouraging research that will continue to improve care and result in a cure for HAE.

- **HAE and Me** (www.haeandme.com)

This online community, launched by ViroPharma Inc. in March, unites teens and adults with HAE through shared experiences to help them better manage their disease. It features information

about HAE, video stories, firsthand tips from patients, and expert advice about living with the disease.

- **HAE Hope** (www.haehope.com)

HAE Hope helps patients and loved ones cope with HAE through helpful tips and information about living with HAE.

- **HAE International Patient Organization** (www.haei.org)

HAEi is a global organization established to promote cooperation, coordination and information sharing between HAE specialists and national HAE patient associations in order to help facilitate the availability of effective diagnoses and management of C1 inhibitor deficiencies throughout the world.

- **U.S. Hereditary Angioedema Association** (www.haea.org)

HAEA is a nonprofit patient advocacy organization dedicated to serving persons with angioedema resulting from C1-Inhibitor deficiency.

ment drugs), which increase the frequency and intensity of HAE attacks. The list of ACE inhibitors to avoid include captopril (Capoten), benazepril (Lotensin), enalapril (Vasotec), lisinopril (Prinivil, Zestril), fosinopril (Monopril), ramipril (Altace), perindopril (Aceon), quinapril (Accupril), moexipril (Univasc) and trandolapril (Mavik).⁵

Living with HAE

Most patients with HAE are able to successfully manage their condition. Nevertheless, HAE is a chronic disease. The severity of the disease, as well as the frequency, type and timing of HAE attacks, vary widely among individuals. And, the pattern of attacks can be inconsistent within any given person, such as having greater or fewer episodes during one life stage compared with another.⁶ According to Diana, "I am both in better shape than I thought, and in worse shape than I thought." She explains that while other HAE patients seem to have more severe attacks to their face and throat more often than she does, she has more overall attacks than normal.

For adults, the key to managing HAE lies in recognizing the specific conditions that trigger attacks and how to handle them. For instance, attacks can be triggered by physical or emotional stress, a change in hormonal levels, and as a result of other medications. For children, the key lies more in communicating with first responders at school and other locations so that they will know what to do when a child with HAE has an attack. It's also a wise idea for children to carry a patient information card with them. For teens, the key is to gradually shift the responsibility for managing their condition from the parents to themselves. This means being able to recognize personal triggers and warning signs, as well as to understand how to deal with the attacks.⁶

While HAE attacks mostly occur suddenly and without warning, some patients are able to recognize the early signs of an attack known as prodromal symptoms. Patients may notice sudden mood changes, rash, irritability, aggressiveness, anxiety, extreme fatigue or a tingling sensation of the skin where the swelling will begin. And, these symptoms may occur minutes or hours before an attack, or they may occur a day or two before a full attack begins. The most serious attacks are intestinal swelling and throat swelling, both of which require immediate medical attention.⁷ In fact, an estimated 15 percent to 33 percent of HAE patients will die as a result of laryngeal edema and asphyxiation.²

The Future of HAE?

In October 2008, Diana attended the U.S. HAEA National Conference. She said she learned that "the quality of life for people with HAE, statistically, is less than that of people with diseases such as Crohn's. I'd once heard that our quality of life is comparable to that of a cancer patient." But, recently, she started taking thyroid medication for "chronic hiving, itching and swelling . . . And, lo, I have not had an attack since I started thyroid medication." Diana says she's lucky: "The people

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[whom] I've met with this disease are far more incapacitated than I ever was by it. They will never see a way out. There is no cure, only imperfect, expensive and life-consuming treatment."

There may not yet be a cure for HAE, but at least now there is treatment. And, with the research being conducted in the area of gene therapy, it is hoped that, one day, there will be a cure. Until then, HAE patients need to ensure they are in the care of physicians experienced in the management of this rare condition, seek out support groups to stay connected and informed (see the sidebar listing social networking sites) and know that they can learn how to individually manage their condition. ■

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