

Snowflake: Just Like Everyone Else, Except Just a Little Bit More So

A psychological and psychosocial overview of Hereditary Angioedema

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MISSION STATEMENT

This paper strives to advance the understanding and treatment of Hereditary Angioedema (HAE) through a blend of psychological, medical, and sociological frameworks. Additionally, it will further weave the tapestry of understanding how the disease, in all of its variety, impacts the affiliated family interactions. Finally, we will provide a patient-based perspective for symptomatically including all subtypes of HAE, including Hereditary Angioedema with Normal C1 Inhibitor (formally known as HAE Type III), for acute and prophylactic treatment.

ABSTRACT

This paper proposes a rule-in/rule-out method of diagnosing Hereditary Angioedema with Normal C1-inhibitor (HAE-NC1-INH). Current methodology often precludes many patients from the compassionate care offered by the use of medications approved to treat Hereditary Angioedema Type I (HAE-I) and Type II (HAE-II). These medications, including Berinert¹, Cinryze², Firazyr³, and Kalbitor⁴, prescribed for either acute or prophylactic indications, have often been denied to the HAE-NC1-INH patient, due both to the lack of suitable diagnostic tests and their high costs. To date, no underlying cause has been identified for HAE-C1INH, and no diagnostic tests exist. It remains a diagnosis of observation and exclusion. To date, many of these patients have been relegated to androgen therapy, which comes with a host of possible negative side effects^{5,6}.

The first part of this paper focuses on the *Stress Response Pattern of Adaptation* to a chronic life-threatening disease; that is, how the individual is left to manage the inherent psychological implications of this life-threatening disease. It further covers the psychosocial functioning of the patient and elucidates the often hidden internal processes that comprise the makeup of the patient and how that patient responds to his or her world, both internally and externally, and the resulting psychosocial pathology.

When the analysis of the psychosocial stress response pattern of adaptation to a chronic, life-threatening disease is accomplished in a thorough and sensitive manner; herein referred to as the *Compassionate Care* model. Compassionate Care uses a two-prong, rule-in/rule-out process designed to allow (if the psychosocial entities complete the picture through illustrations of the emotional and physical presence of the patient upon examination) a clearer path to understanding whether or not the above referenced medications would present relief from the symptoms of Hereditary Angioedema with Normal C1 Inhibitor.

The second part of this paper will shed light on the *orphan disease* aspect common to all forms of HAE. Patients who endure its many and varied symptoms have learned that familial and/or spousal support can be very beneficial to the ongoing maintenance of one's self. We discuss the psychological facets that often leave the patient grieving for a relationship, and how the very nature of HAE can leave the patient feeling frustrated, hurt, abandoned, and alone – except from fellow HAE patients. Discussed at length is the work of coping with grief that the patient must complete in terms of the loss of one's self and family, as well as the loss of participation in many activities that the patient enjoys, but that having HAE precludes. We also discuss the very painful issue of the parent-patient with HAE, who unknowingly passes this autosomal dominant disease on to their children, and

the immense amount of work coping with that grief that must to be accomplished therein.

The third and most important part of this paper is an in-depth case study of an adult female diagnosed with Hereditary Angioedema with Normal C1 Inhibitor. This paper will clearly present the details of the patient's pre- and post-diagnostic information and outline the impact that having a HAE diagnosis has manifested on both her emotional and physical outcomes. This paper does not provide a promise of a cure. However, it will point out the failure(s) of existing diagnostic procedures to properly and fully embrace, with compassionate care, the quality of life issues that HAE-NC1-INH patients face if they wish to bring their quality of life up to that of HAE-I and HAE-II patients. Although this paper does not propose to be a defining manuscript on HAE, it is our goal that it be viewed as a trail which can be widened to a road, continuing the process of understanding and assisting the HAE patient to a better tomorrow. Furthermore, it seeks to pass on to physicians, nurses, and those living and working with HAE to better understand and treat the total picture of the HAE patient and his or her world.

HEREDITARY ANGIOEDEMA TYPE IDENTIFICATION

Hereditary Angioedema (HAE) is a rare condition, with an estimated incidence of 1 case per 50,000 persons, with no known differences among ethnic groups⁷. There are multiple types of HAE, with each case currently identified by one of three designations: Hereditary Angioedema Type I (HAE-I), Hereditary Type II (HAE-II), and Hereditary Angioedema with Normal C1-inhibitor (HAE-NC1-INH).

Common Symptoms

Common symptoms of all types of HAE include painful, unpredictable, recurrent attacks of inflammation and swelling of the hands, feet, face, abdomen, urogenital tract, and larynx. The swelling can be both disfiguring and painful. Abdominal swelling typically involves intense pain, vomiting and diarrhea. Laryngeal attacks can be life-threatening if the swelling compromises the airway⁸. Symptoms usually appear early in life, often in childhood, and may increase in severity after puberty⁹. Episodes may be spontaneous or triggered by physical trauma or emotional stress.

Causes

Patients with HAE-I suffer from a deficiency of a protein called C1-inhibitor. Those with HAE-II tend to have normal, or even elevated, levels of C1-inhibitor; it just doesn't function correctly.

C1-inhibitor is one of over 25 proteins and protein fragments that make up the *complement system*. The complement system aids the body in identifying, killing, and clearing invading cells and pathogens. It is part of the *innate immune system*, that part of the immune system that is not adaptable and does not change over the course of one's lifetime. It serves as the body's first line of defense against invading organisms. Its major functions are:

- Acting as a physical and chemical barrier to infections agent.
- Directing immune cells to the site of an infection.
- Identification and removal of foreign substances found in the body.
- Activation of the *adaptive immune system*. The adaptive immune system is the part of the immune system we typically think of as being responsible for adapting to, eliminating, and preventing disease-causing pathogens from flourishing within the body.
- Activation of the complement system.

C1-inhibitor is a protease inhibitor whose main function is the inhibition of the complement system to prevent its spontaneous activation – activation in the absence of a corresponding threat to the body. Spontaneous activation of the complement system contributes to the out-of-control swelling that is the hallmark of HAE. C1-

inhibitor plays an important role in HAE, and forms the basis for two of the medications, Berinert and Cinryze, currently approved for treatment of HAE in the United States.

The cause of HAE is can be traced to one of more than 200 identified mutations of the human C1-inhibitor gene (SERPING1), located on the eleventh chromosome¹⁰. HAE (at least in the cases of HAE-I and HAE-II) is an autosomal dominant disorder. If a disease is autosomal dominant, it means you only need to get the abnormal **gene** from one parent in order for you to inherit the disease. One of the parents may often have the disease.

Inheriting a disease, condition, or trait depends on the type of chromosome affected (autosomal or sex chromosome). It also depends on whether the trait is dominant or recessive. A single, abnormal gene on one of the first 22 non-sex chromosomes from either parent can cause an autosomal disorder. Dominant inheritance means an abnormal gene from one parent can cause disease, even though the matching gene from the other parent is normal. The abnormal gene dominates.

A child's risk is independent of whether a sibling has the disorder or not. For example, if the first child has the disorder, the next child has the same 50% risk of inheriting the disorder. Children who do not inherit the abnormal gene will not develop or pass on the disease¹¹.

The genetic defect may also be caused by spontaneous mutations, and it is estimated that 20% to 25% of all HAE cases occur in patients with no family history of the disease¹². However, if a child has a disorder that is typically inherited in an autosomal dominant manner, like HAE, then the parents should also be tested for the abnormal gene.

Diagnostic Tests

In attempting to diagnose HAE, a doctor will often look at three diagnostic tests. The first of these tests looks at the level of another complement system protein, C4. In patients with HAE, the level of C4 is almost always low. If testing shows that C4 is low, additional tests are used to look at both the quantitative and functional levels of C1-inhibitor, with the results allowing the doctor to differentiate between Hereditary Angioedema Types I and II⁹. At this time, there is no diagnostic test for Hereditary Angioedema with Normal C1-Inhibitor.

Hereditary Angioedema, Type I (HAE-I)

Patients diagnosed with HAE-I possess lower than normal levels of C1-inhibitor. Patients with this form of the disease make up 80 to 85% of all HAE cases¹³.

Hereditary Angioedema, Type II (HAE-II)

Patients diagnosed with HAE-II possess normal, or even elevated, levels of C1-inhibitor. However, the C1-inhibitor that is produced does not function correctly, leading to the same set of symptoms seen in patients with HAE-I. This form of the disease is more rare, comprising 15% of all HAE cases⁹.

Hereditary Angioedema, Normal C1-inhibitor (HAE-NC-INH)

HAE-NC-INH is quite rare. Patients with this form of the disease experience symptoms quite similar to those suffering from HAE-I and HAE-II. In addition, the tongue is considerably more often affected, with recurrent tongue swelling observed in many patients, and considered to be a cardinal symptom of the disorder¹⁴. In some patients, the disease appears to be estrogen dependent, often associated with pregnancy, use of estrogen-containing oral contraceptives, or hormone replacement therapy¹⁵.

Unlike patients with HAE-I or HAE-II, those with HAE-NC1-INH have normal levels of functional C1-inhibitor. A small number of cases have been shown to be associated with mutations in the Factor XII gene, though this has not been proven to be the cause of the condition. No concrete underlying cause for the disorder has been identified, and there remains no definitive diagnostic test for HAE-NC-INH. A consensus of an international panel of experts in HAE have proposed a set of criteria aimed at helping physicians diagnose HAE with Normal C1-inhibitor¹⁶. These include:

1. A history of recurrent angioedema in the absence of concomitant hives or concomitant use of medication known to cause angioedema.
2. Documented normal or near normal C4, C1-inhibitor quantity, and C1-inhibitor function.
3. One of the following:
 - Demonstration of a Factor XII mutation that is associated with the disease.
 - A positive family history of angioedema and documented evidence of lack of efficacy of chronic high-dose antihistamine therapy.

Treatments

Androgens (also known as anabolic steroids) such as danazol, oxandrolone and stanozolol, have historically been the most commonly prescribed prophylactic HAE therapies^{17,18}. Although anabolic steroids have been shown to be useful in increasing C1-inhibitor levels and thereby relieving symptoms in some, they carry with them the risk of a number of adverse side effects, including weight gain, acne, masculinization, altered libido, menstrual irregularities, headaches, depression,

fatigue, lipid abnormalities, hypertension, cholestasis, increased liver enzymes, peliosis hepatitis, and hepatocellular adenomas^{5, 7,19,20,21,22,23,24}. Several of these adverse effects indicate androgens may not be well tolerated by many female patients. Additionally, these drugs should not be used to treat children, who may suffer attacks at the same frequency and severity as adults, given their potential to affect growth and development. Research indicates that the majority of patients treated with anabolic steroids still experience breakthrough attacks, including laryngeal or abdominal attacks that may require hospitalization¹⁹.

The U.S. Food and Drug Administration (FDA) has recently approved four new treatments for HAE. Berinert a concentrated C1-inhibitor preparations derived from human plasma, Kalbitor, a kallikrein inhibitor, and Firazyr, a bradykinin-receptor antagonist, were approved for the treatment of acute HAE attacks^{1,3,4}. Cinryze, also a plasma-derived C1-inhibitor concentrate, was approved as a prophylactic treatment, intended to prevent or reduce the frequency and severity of HAE attacks². These new products have given patients and their physicians new options for developing a treatment plan tailored to meet each patient's unique needs – one not dependent on the use of androgens.

While these new treatments are readily available for those suffering from HAE-I and HAE-II, treatment options not so clear for HAE-NC-INH patients. With lack of a definitive cause, few diagnostic tools, and difficulty in obtaining a diagnosis, these patients have found it much harder to gain access to these treatments. Physicians may their efficacy, while insurance companies often balk at approving reimbursement without a definitive diagnosis.

Research into the possible treatments for this rare form of HAE continues. Published cases document response to these FDA-approved HAE therapies. It must be noted that all three HAE types have a tendency to exhibit the same symptom expression in terms of psychosocial and bodily reactions to the presentation of the disease. As such, there tends to be a relatively standardized manner of response to the affliction of HAE and it's remarkable ability to explode into presentation. One of the best diagnostic tools termed and explained herein is the *Stress Response Pattern of Adaptation* to chronic disease with life threat. This process is critical to the individual's ability to respond to this disease. The psychosocial paradigm of coronary artery disease, for example, illuminates the impact of disease and it's relative management to and for the patient.

THE NEED FOR STANDARDIZED PROTOCOL

Due to the unpredictable severity and the episodic nature and presentation of HAE, it is necessary to have in place a pragmatic and organized manner of preparedness

for medical management of this disease with either prophylactic and/or rescue medications. In addition, it is also necessary to include in this protocol the risk vs. benefits of androgen therapy-including its side effects and that the services to the patient be laid out as thoroughly as possible

Once the patient receives a proper diagnosis indicating HAE and receives the prescribed medication, it becomes incumbent upon the patient, in conjunction with those in the treatment chain, to adapt and adopt a standardized protocol for dealing with the severity of the presentation of HAE within the frame of reference of the patient's severity of symptoms. Such a protocol should include, but is not limited to, the interaction and input of the patient's primary care provider (PCP) with the emergency services chain in regard to the patient's location and access to treatment. This emergency services chain would be at its zenith if laryngeal swelling were also included in the patient's pattern of presentation. In an effort to further enhance the appropriate treatment of the patient, notification and education of local emergency ambulance personnel, emergency room services, nurses, and associated healthcare providers in the appropriate care of the HAE patient should be provided. An approved list of family and team members who may find themselves needing to speak and advocate for the patient should also be on file with these providers. It is at this critical point in the care of an HAE patient that the need for concise, clear instruction and communication becomes most crucial.

Identification of a medical emergency becomes the single most critical point in the care of the HAE patient. Presentation of the abdominal swelling, although, in some cases not as seriously urgent as a laryngeal involvement, requires protocol for the immediate transfer of the patient to a medical facility and the essential education and training of family and emergency room personnel for management of pain and dehydration. For example, the treating medical team should be aware of the exacerbation potential of enemas, colonoscopy, or other invasive procedures in the colorectal area as this type of intervention will worsen the swelling and further occlude the bowel. Due to the excruciating nature of pain experienced, the HAE patient presenting with abdominal complex swelling is most often mischaracterized as "drug seeking" in nature, often due to the lack of education of HAE symptoms on the part of the medical staff. Similarly, in years past, patients suffering from sickle cell anemia and hemophilia experienced similar treatment.

Both the physician and patient must address all possible presentations of HAE in order to provide cohesive and credible treatment in a crisis. It is the purview of the patient's PCP or HAE specialist to advise and assist planning of a working protocol to be executed upon arrival of the patient at the medical facility. It would also be necessary for the physician, given the team approach, to include pharmacy personnel in assuring the availability of prescribed medication. In a working protocol, personnel included in the planning and education of HAE management

should include all emergency room physicians, pharmacy, respiratory therapy, and nursing staff.

PSYCHOSOCIAL ASPECTS OF HAE

Addressing the psychosocial elements endemic to life-threatening illness is a useful in presenting a diagnostic profile of the disease as it presents in the patient. As with survivors of trauma, patients with the laryngeal swelling exhibit symptomatology of post-traumatic stress disorder (PTSD), which then permeates how the patient views and responds to the world, both internal and external. Similar to sufferers of coronary artery disease, post heart attack, there are inherent issues with changing a patient's adaptation and interaction to life with a serious, chronic illness. Specifically, strong issues of depression, depersonalization, a sense of foreshortened future, relationship difficulties, inability to gain or hold employment, anxiety, and sexual dysfunction are all part of the shared stress pattern of adaptation to the chronic life-threatening nature of HAE²⁵.

Because of the enormous amount of stress present within an affected family, we must address the impact of the diagnosis and manifestation of HAE on the patient, as well as the strong similarities with the symptomatology of PTSD. We know that humans are susceptible to responses to traumatic events. Since 1980, the American Psychiatric Association has held within its purview the impact of trauma upon survivors of traumatic events. The most difficult form of trauma is noted to be that from "the hand of another person" such as combat, rape, or brutal assault. The benign trauma thrust upon the person is often referred to as an "act of God" e.g., life-threatening disease, severe weather trauma, and most automobile accidents. The impact of the trauma manifest with a HAE diagnosis on a patient's life carries with it repeated life-threatening events and a lack of ability to psychologically prepare for the severe and potentially life-threatening presentation of laryngeal complex swelling.

Depression, anxiety, reliving traumatic events, psychosocial impairment and a sense of foreshortened future, are common to both HAE and PTSD. The psychosocial elements associated with HAE are a response to a disease that refuses to play by the rules. There are no rules and the more the patient attempts to find or make rules that will prevent the presentations, the more frustration the patient feels, which in turn often creates a more frequent and severe presentation. Laryngeal swelling, when fully expressed, is life-threatening due to total blockage of the airway. It is the worst manifestation of HAE. Moreover, this presentation leaves the patient with a life expectancy of minutes at its most severe. This life expectancy issue was most recently addressed by The United States (US) HAE Association President, Anthony Castaldo, in his testimony to the Appropriations subcommittee for HAE

Research funding in June of 2012 noted the mortality rates for HAE patients to be greater than 30% overall²⁶.

OVERVIEW OF LARYNGEAL COMPLEX SWELLING

The laryngeal complex swell is perhaps the most severe and dreaded presentation of HAE, due to the high rate of morbidity and mortality. HAE is known to be highly nomadic in its ability to present in one location of soft tissue and within moments move elsewhere. The patient with a seemingly benign bump, scratch, or minor cut on an extremity may suddenly be thrust into what literally becomes a life or death situation. Any presentation of face, tongue or esophagus may, without warning, evolve into laryngeal swelling and, with many, transform again within moments to an immediate life threat. This sudden presentation leaves the patient with great anxiety and fear of the outcome, as the potential for death is imminent. Once the patient has experienced this level of presentation, any noticeable bump, scratch or hit revives memories of past realities. Thus, the resulting anxiety causes a more intense adrenal situational reaction, commonly known as fight or flight, in the patient as the incumbent stress of the situation increases the adrenal response and the realized fear. This event becomes locked in the patient's memory and impacts all future presentations with the fear that they, too, will quickly escalate into a life-threatening situation. Those who have not experienced this sort of trauma cannot understand or appreciate its impact.

Further complicating the psychological aspects involved in a severe HAE presentation is the propensity of the patient to depersonalize, minimize, and manifest significant depression. This response to the threat of laryngeal involvement occurs for some as frequently as once per week. Life is often dependent on medical personnel unfamiliar with HAE, required to treat a disease presentation that few have read about, and fewer still have ever seen. This leaves the treatment milieu incomplete at best. The response pattern of adaptation becomes complicated by patients who no longer seek treatment in the emergency room because of their level of frustration over the treatment received they have received in the past. A patient may reach a point of ignoring or *daring* the presentation of laryngeal swelling by medicating with a sleep aid and going to bed, thereby risking death by denying the severity of the disease presentation. This depersonalization and cavalier attitude toward the disease demonstrates the depressive level of the patient's inability to adapt. Historically, the response by medical staff is to treat the patient with an ineffective allergy/anaphylaxis protocol, often leaving the patient feeling terribly

alone and helpless. Further, hopelessness leads to the isolation, depersonalization, and depression endemic in chronic life-threatening illness.

ABDOMINAL COMPLEX SWELLING

For those HAE patients who do not experience the severity of laryngeal complex swelling, the abdominal complex swelling is described as having a tremendous physical and emotional impact on the patient and family's everyday life. While typically not life-threatening, the abdominal swelling can progress rapidly to the point of excruciating pain, hypotension, dehydration, and hypovolemic shock that can, in rare instances, also lead to death. Many patients experience shortness of breath due to the pressure on the diaphragm and lungs, as well as bowel obstruction, nausea, and projectile vomiting. There have also been reports by patients of hematomas in the chest musculature from the severity of the vomiting. Many female patients have stated that the severity of pain from abdominal swelling is far beyond that of childbirth without anesthetic. The pain level in HAE patients has, historically, caused many HAE patients to endure being described by ER physicians and nurses as drug seeking due to the high level of pain reported. It is especially difficult to the "Highly Sensitive Person" (HSP), a personality type who is more susceptible to severe pain, for which HAE may become even more debilitating. Due to past experiences, the HSP depersonalizes the pain while simultaneously seeking the understanding and approbation of that pain by family and physicians.

Within the HAE community, many other symptoms have been described both pre- and post-presentation. Sexual dysfunction from the HAE presentation becomes a serious and painful issue for both male and female patients and their partners. For the uncircumcised male, the swelling of and around the foreskin as well as the entire penile and scrotal tissue makes coitus painful and often impossible. This type of swelling also prohibits walking, working and sometimes prevents the patient from going out in public at all. The female patient experiences genital swelling that also prohibits sexual activity and may begin before, during or after coitus. When you think in terms of abdominal or genital swelling you must also be aware that it may lead to obstruction of the bowel or urethra, respectively, causing yet another trip to the hospital. It is not atypical for the abdominal or genital swell to nomadically migrate in an instant to the throat and/or other extremities. Sometimes swelling may even be triggered by trivial tasks – brushing the teeth, for example. Dental procedures are particularly terrifying for many HAE patients, as the invasiveness, further stimulated by the anxiety of the patient during the procedure, offers potentially life-threatening consequences.

A major issue in the diagnosis and treatment of the HAE patient is the need for the healthcare provider to have awareness of the variety of HAE's presentation. The swelling among HAE patients often shows highly individualistic forms of expression, even within families. One may use the analogy of the snowflake. From a distance, all snowflakes appear to be alike. However, close inspection demonstrates subtle but highly individualistic characteristics. For that specific reason, the HAE-NC1-INH patient is essentially excluded from the newer medications primarily aimed at HAE-I and HAE-II patients, easily diagnosed by their inadequate or dysfunctional C1-inhibitor. Insurance regulations thus far prohibit use of these medications off-label to address the possibility that the HAE-NC1-INH patient may have their presentations diminished, or even terminated, when using prophylactic medications currently on the market.

It is the position of these authors that, beside and exclusive of the typical biochemical blood evaluation of the HAE-NC1-INH patient, a more compassionate care, second-pole diagnostic evaluation aid in a rule-in or rule-out manner be evaluated for the efficacy of currently available HAE drugs, both rescue and prophylactic. It would appear the cost analysis issue is but one of the many barriers noted as having a major impact on drug availability for the HAE-C1-INH patient. It is our opinion that all patients displaying the symptomatology of angioedema are deserving of the compassionate care of their physicians. It is not acceptable to leave ANY angioedema patient to the realm of allergy and anaphylaxis treatments, or androgens and their inherent side effects. The compassionate care model would, therefore, provide a dose-limited course of treatment using the already approved medications that are available to HAE-I and HAE-II patients. The patient's physicians, nurses, and pharmaceutical case managers should monitor this treatment approach. Attention should be given to the cost of these medications and, as such, assistance should be obtained by every means available in order to provide an improvement in the patient's quality of life. Based on current protocols, this level of compassionate care is not offered to all patients suffering with the complexity of this deadly orphan disease.

ANXIETY AND PSYCHOSOCIAL ASPECTS OF HAE

Deeply entrenched within the diagnostic picture of HAE is the *Stress Response Pattern of Adaptation* to a chronic life threatening illness. The medical-psychiatric co-morbidity describes the relationship between medical disease and psychological functioning. It is a complex but important subject as chronic life-threatening illness clearly presents a challenge to psychosocial adjustment for both patient and family simultaneously. The familial/family impact and potentiality of pathological outcome of HAE diagnosis will be illuminated and illustrated in a further section.

This psychosocial adjustment to a diagnosis of HAE influences onset course, treatment efficacy, and management of a chronic illness, which ultimately bears heavily upon the patient's quality of life. The concept of psychosocial adjustment includes anxiety, coping skills, depression, insomnia, and memory and other cognitive difficulties. This psychological adjustment also includes the affective response to a potential of threat to life, a common element in those HAE patients who present with laryngeal complex swelling. Other specific symptoms comprise the presentation of the disease, however, the laryngeal complex swelling facet of the disease is highly traumatic and the resulting psychological impact on the patient fits directly into the paradigm of PTSD. Therefore, specific attention is given in this article to highlighting the stress related to a HAE diagnosis because it is necessary for health-care providers and their patients to be aware of its impact. We will detail the connection between PTSD and the HAE diagnosis, which commonly recurs, and illustrate how the stressors of the disease are adapted to and modified by the Stress Response Pattern of Adaptation.

This Stress Response Pattern of Adaptation simply expresses the manner in which the patient binds his anxiety to the disease, as well as the impact of the disease on the totality of the family, including isolation, withdrawal, depression, and sense of for-shortened future, emotional liability, and sexual intimacy. The capacity to fight intellectually no longer exists, leaving flight as the only recourse. The family support system in the HAE patient is rife with potential pitfalls and psychological support possibilities that either add to the patient's ability to manifest the integration of the disease or its presentations into the cauldron of the family dynamic. In many cases, the patient may find that the support he/she believed to exist within the family or primary support system has been ameliorated by fatigue from the demands of the disease on the family structure.

This existential crisis of losing support, or finding support to have evaporated, serves to trigger a tremendous sense of loss, abandonment, and betrayal in the patient and may serve as to trigger the disease when the emotional crisis is brought to bear. If the patient believes the family relationship is safe and reliable, and then discovers that to be in a myth or fictitious wish, the patient is then left vulnerable to a deeply wounded sense of self. This situation in turn leaves the HSP feeling left without an anchor in a sea of emotion. The circular pattern of prodromal behavior and resulting aloneness may trigger swell after swell at varying locations and intensity in a seemingly unending pattern. The result may well be the use of drugs outside of prescribed medications, overuse of prescribed medications, and a host of unhealthy psychological defense mechanisms such as depersonalization, denial, and aggressive attachment to others the patient may identify as "like themselves"²⁵.

TRAUMA ISSUES OF HAE

The death of a fellow HAE colleague as the result of a laryngeal swelling will undoubtedly bring back the tangible fears of other HAE patients who have experienced this sort of attack. Once a patient has experienced or witnessed the effects of a laryngeal swelling and all the treatments, fears and emotions that go with it, there is a realization that they are facing death and it remains with them for their lifetime. The unpredictability of this aspect of the disease keeps the patient psychologically off-balance, as fear and anxiety begin to build in earnest. For those patients with this presentation history, the unexpected death of a fellow HAE colleague will trigger heightened anxiety and memories of the helplessness they have personally experienced. Feeling a tremendous sense of helplessness over the sudden death, these memories stir a range of response patterns, of which, anxiety over going to sleep that night or subsequent nights becomes evident. The patient may also feel an overwhelming sense of helplessness. The intensity of the helplessness will always revivify, re-evoked personal memories of such past life threats or self-endured events creating a stew of emotion with extreme potentiation for causing the very entity one was afraid of to begin again.

Within the madness of the paradigm of the HAE Stress Response Pattern of Adaptation, is the need for self-soothing of the anxiety and other delineated entities. It is typical, and for some, normal to attend to this self-soothing within the framework of one's belief system in a higher power. This higher power is often described or referred to as God, the great spirit, or other religious deity common to the belief system one grew up in or has elected to his/her personal tastes. As previously noted, the more severe the life threat and loss of innocence, typically the stronger one's faith is, it would appear to be clung to in order to provide a safer sense of well-being. It would be atypical for a human being, or a trauma survivor for that matter, to not have some form of spiritual or religious paradigm with which one can face the unrepentant, unpredictable, and/or undefeatable entity of life threat associated with HAE. Man just isn't typically made that way. Military survivors of the trauma of combat speak eloquently of "there are no atheists in a foxhole". The extension of that rubric would appear to be present with the HAE patient. There are many and diverse avenues of dealing with chronic life threat and in one's attempt at self-soothing.

Within the paradigm of HAE there exists a support system of fellow travelers with the HAE as a common base. (It should be noted that this very support base can become an issue of jealousy within the relationship between patient and non-patient spouse). Jealousy over the amount of time given to a support community begins to be perceived as a replacement for family interactions. The support community typically uses religious or spiritual language in receipt or expression of comfort from the support group. In group cohesion, there is no right or wrong methodology. The

common ground of expression of caring and concern tends to replace specificity of one manner of expressing concern and/or hope and being cared for. All help is good help and comes from the heart, if shared in this manner. Many times, upon having endured the symptoms of HAE for years and suddenly finding a name and criteria for the disease, the patient is often noted to be in the initial stage of grief termed *Outcry*.

The Outcry stage of grief may take many forms, internal or external or both simultaneously. It is not uncommon to see the patient stuck squarely in this phase of grief. One of the variables in moving through stages of grief is how the individual learned from their parents (or caregiver) to manage strong emotions, be it striking out in anger, or by internalizing such as depression. The range of outcry may keep the patient telling and retelling anyone and everyone about the “rare” disease they have. This retelling internally expresses a need for soothing and empathy and is also recognized as a form of obsessive compulsion, which, if retold often enough and in just the right manner it will either go away or be internalized as a reality. If the patient did not receive it in sufficient quantities as a child, the need will be greater to scream the news of the diagnosis and it becomes the largest thing in one’s life. In this manner, it could be said it is “splattered on those most close to him”. The splatter effect is termed as such because as the patient is busy getting his needs met for recognition and empathy, all else is negated and others may shrink from their presence. Especially cogent would be the HSP, once called neurotic, when the school of thought ran towards identifying outcry as something negative. Similarly, HAE was considered a neurosis called angio-neurotic edema prior to being known as the more acceptable HAE²⁵.

The sublimation of the splatter effect is in essence, playing on the sympathies of others. It is the patient effectively saying that "I cannot tolerate nor handle this entity and I must scream my pain until I receive some type of response". This splattering is accomplished with little knowledge of exactly what is needed from others, or simply flat out raging at the unfairness in having the disease and having no one to assist help manage it. Many patients are not aware of the impact of the *splatter effect*. In truth, everything we do in life “splatters” on others, thus lending full credence to Newtonian Law—“for every action there is an equal and opposite reaction”. Children live what they learn, and the response patterns of adaptation by parents who are stuck in the negatively charged pattern of outcry learn that the manner of expression by the parent figure is appropriate, no matter how abnormal and unhealthy it may NOT be. The messages children receive from parent figures in their limited world are called *introjections*. These often unintended messages stay with the child and are internalized as an acceptable manner of response, as illustrated by the parent figures.

Should the offspring of an HAE patient also be diagnosed with the disease, the emotional reaction of the patient-parent will include elements of emotional liability, helplessness, and guilt, at minimum. The requisite stages of grief will understandably be more protracted and emotionally loaded. This splatter effect will add to the trauma of the disease and the ability to normalize it into an already difficult road to travel for youth and adult. The suggested path for the patient/parent is one of seeking a solid support base or perhaps more ideally, seeking help from an enlightened PCP who can discern the need for a referral to a professional who will assist in the process in order to better endure this emotionally laden situation. The splatter effect does no one any good, unresolved.

THE BLOWFISH PHENOMANOM

Blowfish is an innocuous term utilized to alert the HAE patient of an unnoticed pending presentation/episode of HAE. Many times, preceding the presentation, small, seemingly unnoticeable to the patient, cognitive aberrations, slight changes in mood or other physical changes, can be noted by family members or others close to the patient. Usage of the term, or any mutually agreed upon “safe” word serves as a non-threatening notice to the patient that whatever preparatory manifestations are usually taken for the HAE, now is the time to commence.

Many patients tire of the disease presentations, and as such, may tend to depersonalize or refuse to cognitively attend to their body messages, as the disease can-and does-sneak up on the patient. If the patient is not on a prophylactic drug, as is the usual case for the HAE-NC1-INH patient, there are many possible steps to take to try to help minimize the presentation. For example, if a presentation is imminent, travel may not be such a good idea, nor is being very far from a hospital setting since there is absolutely no way to predict the oncoming severity of the presentation, leaving both patient and family feeling prisoner to the disease and its ramifications. Another healthy component to usage of a safe word is that it may allow family members to all participate in the care of the disease and, therefore, potentiate the outcome for both the patient and the family. In many cases, the family dynamic may become strained by the heavy burden this disease places on personal interactions when in full bloom.

GRIEF

Inherent in the diagnostic picture of a debilitating and life threatening disease such as HAE is the grief work that must be done. From the shock and denial stages of

grief, to acceptance and resolution lies a long and difficult path. More often than not, those patients recently given the diagnosis of HAE are told by their health-care provider team to suggest that their own children not have children due to the hereditary nature of this disease. The grief work is paramount to achieving some form of resolution or acceptance of the disease and, therefore, its impact on the severity of the presentation of the disease. As mentioned above, the knowledge that one may have passed on the disease to one's children is extremely difficult for the patient to achieve peace and closure on. Knowing the multi-faceted presentation of the disease, the nomadic nature of it, and the physical pain involved-not to mention the potentiation of life threat in one's own children-cuts to the very core of the patient and, at times, increases the severity of the presentation through exacerbation of emotional duress²⁵.

Any survivor of trauma, be it of combat or chronic life threat or disease such as HAE, will deeply understand and identify with Job's words to his God as he endured the pain, separation and loss of value that he held dear. The words of Job become an anthem to the survivors of chronic life threat:

*And now the life in me trickles away,
Days of grief had gripped me,
At nighttime, sickness saps my bones
I am gnawed by wounds that never sleep,
With immense power it has caught me by the clothes
Clutching at the collar of my coat
It has thrown me into the mud
Where I am no better than dust and ashes
I cry to you, and you give me no answer;
I stand before you, but you take no notice.
You have grown cruel in your dealing with me,
Your hand lies on me, heavy and hostile.
You carry me up to ride the wind,
Tossing me about in a tempest
I know it is to death that you are taking me,*

The common meeting ground of all that lives²⁷.

Job may well have been speaking for the HAE patients as he deals with and endures the multi-faceted presentations of the disease and it's nomadic nature of freely roaming the system wherever and whenever it desires. From the very initial symptom to the pronunciation and description of the HAE diagnoses, the pendulum between life and death swings with no respite from the fear, terror, stress on the mind and body, and the abject loneliness for many who find a need for some long lost sense of normalcy.

For many confirmed HAE patients, having a name put on the very strange symptoms they had been experiencing but had no cohesive explanation nor diagnoses for is initially a relief, followed by grief, and anger for the way they have been treated. Suddenly there is horror in knowing that your children and their children may be involved as well. Many patients were seen as psychologically damaged due to the strangeness of the symptoms, which fit no known disease. Many report an initial lack of understanding by health-care providers of the strange symptoms with apparently no answers. Suddenly a diagnosis of HAE is afforded, and the first cognitive thought is I'm not crazy, as I had feared, and in many cases, was told.

SNOWFLAKE

A Case Study

Thursday, November 1, 2007

Thank you Jeff for the swift response, in answer to your questions... The outward abdominal swelling has been happening for almost eight years now. Prior to that I can only tell you that I was told by my family (mom and grandmother) that I have "the belly". They have whatever this is too and it affects each of us differently. This thing seems to evolve from my grandmother to some of her children but not all of them, some male, some female. As a six-year-old child, I remember vividly lying in the dirt on the playground with severe abdominal pain while the others (teachers included) stepped over me thinking it was attention-seeking behavior because it happened often. The pain was and still is worse than any labor I've ever had with childbirth. I had three children without epidural (now that's nuts), two were Lamaze births. Stress? Sure, I've had plenty. I've taken steps to reduce my stress where it's possible to do so. However, I swell whenever and wherever. I swelled in Hawaii, having a great time. I can tell you that stress exacerbates the situation and greatly increases the chance of a sudden swell. You tell me bad news and I will puff up like a toad right in front of you. I have tested C1 functional and absolute, both normal. I

have had computed tomography (CT) as well as a gastro-intestinal (GI) workup with upright abdomen during a swell and it is all normal. How is it possible to have a picture of my belly that is normally 28 inches at the waist now blown up to 38 inches within an hour and on film nothing stands out? No fluid, no pooh, no gas. Everything looks like a normal belly of an obese person; so what exactly is the swelling?

I've had consults with obstetrician/gynecologists, gastroenterologists, and Allergy and Immunology specialists. All to no avail! I am starting over with GI specialists presently. Is there a study... any study that my family might qualify for? I have children and grandchildren that may already be following in my footsteps. What can I do for them? The allergy specialist has told me that my symptoms/presentation does not fit HAE. Okay, then what is it? I have been told that this is all in my head. Great, sign me up, there's a treatment for that. I have been told it's not gynecology-related. So, what is it?

Then, as the diagnosis is understood and what it means to the patient and the family, the depression and frustration with anger hits. The collateral damage begins to accumulate and there are suddenly consequences to caring. As time and presentation of the disease march on, the relationship the patient might have felt to be supportive, suddenly begins to disappear due to the overwhelming nature of cognitively and physically coping with the disease. The anxiety, in relation to the disease itself and family support begins to overtake the patient and depression becomes larger, witnessing to the inordinate amount of grief work to be done.

The HAE patient who deals with the laryngeal complex swelling presentation of the disease will face the probability of intubation, terrifying emergency room visits at which the caregivers may or may not understand the severity, and chronicity of this dreaded presentation. Many patients have lost their lives during a presentation of this disease without the means to stop it. Many who have experienced the terrifying suddenness of the onset of swelling to the complete closure of the throat with the subsequent inability to breathe then experience the sudden terror that kicks in. The struggle then really begins as perhaps does the individual given a death sentence. Plato spoke with elegance to this situation writing in "The Republic" (regarding Socrates) this death sentence is announced to him: that instant he dies. For the one who does not understand the whole of the spirit it is required for dying, and that the hero always dies before he dies, that man will not get very far with his concept of life.

Although Socrates' death was dictated by the state, the process remains scarily similar to the HAE patient who knows what the potential presentation of laryngeal complex swelling may well present. Should the previous words seem melodramatic, there is true grief work to be done within the individual patient and, in a most serious fashion, for the family as well. The potentiation for the loss of life due to HAE in the patient stands to create tremendous helplessness and activates the

psychosocial stress pattern of adaptation of this orphan disease, long thought to be a psychiatric manifestation.

Aristotle wrote that "philosophy is learning how to die". From the first manifestations of the symptoms of HAE as a primary diagnosis until the disease and its potentiation of outcome for the patient, as with any life threatening disease such as leukemia or hemophilia (to include, for example, male or female breast cancer or testicular cancer), the patient is confronted with highly specific knowledge of the temporal nature of life. In short, it becomes highly personal. If the familial nature of the disease is noted in one's offspring, the grief work needed in order to come to a sense of peace and acceptance becomes exponentially more difficult. The totality of one's being is enmeshed in the psychosocial Stress Pattern of Adaptation and cries for support as well as all of the previously noted challenges. If the cauldron of family support is not found to be present to provide safety for the patient, this fracture in trust is such a huge blockage to dealing with the standard stages of grief: 1) shock, numbness, denial, and disbelief, 2) anger, guilt, 3) bargaining, 4) pining, yearning, depression, and finally 5) resolution.

These stages can be obvious to the patient, family, and caregivers, or they may not be, given the relative nature of treatment. This grief work is highly dependent on the individual and on the nature of the severity and support available to the patient. Sleeplessness, irritability, anxiety, or apathy may be the chief evidence of an individual's grief. Still, other individuals may act as if nothing at all has changed and adamantly refuse to recognize or deal with the grief. Any loss is change and any change must be grieved. Loss can speak to the certainty of health of the individual-or child, or family member, and the loss of innocence.

As the rape trauma victim(virgin at the time of the rape) must deal not only with the physicality of the act, so too must they deal with the difficulty of the loss of innocence. The intensity of grief varies with the significance of that which was lost. Generally, grief is felt intensely when a loss is fresh or new. Those with HAE and its potentiation for life threat, must continually deal with "anticipatory grief", i.e., always looking over one's shoulder at any indicator of the HAE presentation in order to maintain some sense of control in a personal world gone awry and mad. This static anxiety begins with the first sign of swelling in any anatomical location and continues as the patient becomes aware of the ever present nomadic nature of this orphan disease HAE in its transitory nature can move from any extremity or abdomen directly to the airway compromising the ability to breathe and creating an obviously deadly situation at any given moment.

As detailed above, if the child of the patient is found to have inherited this autosomal dominant disorder, the parent/patient has even more grief work to do – both actual and anticipatory in nature. The familial response of the spouse may begin as supportive, but due to limited medical knowledge of this disease and its

symptomatology, the patient may be considered a drug seeker as he or she attempts to find pain relief from the serious degree of pain in an abdominal presentation. The patient who may or may not have been able to achieve the resolution stage of the endemic grief process leaves because of the constant nature of the disease, compounded by the potential loss of spouse through fatigue in dealing with the seemingly never-ending battles with the disease presentations. The patient may find the relationship drifting as the first sensation of something missing. An accompanying lack of physical intimacy may present the patient with a foreboding sensation of loss and possible anticipatory grief. These losses are stacked upon the patient, most likely now stuck deeply in the outcry and anger phases of grief. No sense of normalcy is found at this point and a pathological stress pattern of adaptation is the only outcome. Symptoms of this psychosocial stratum are impacted depression, heightened anxiety, sleeplessness, and a terrorized response to the announcement of another HAE patient's death due to the disease.

The totality of the process illuminated above becomes a psychic whirlwind the patient cannot escape from or find psychological safety to move through the stages of the grief process to an integrated level of the stress response pattern of adaptation. One of the major tactics used by many HAE patients is the depersonalization of self and the disease, common to trauma survivors, in order to diminish the impact of the physical and emotional pain incurred in the presentation. Massive swelling of extremities like hands, feet or especially the facial features of lips or eyelids can be so psychically debilitating in its distortion from normal, that the choice comes down to hiding from everyday life and withdrawing or depersonalization and denying the sense of shame the disease can trigger.

The wide range of symptoms expressed by HAE patients is similar from patient to patient; however, these are often different in either shape or size of their scope and presentation. All presentations evoke the psychosocial entities of withdrawal and helplessness. The helplessness in the here and now RE-evokes and revivifies the similar previous helplessness and the need for one's self-soothing becomes even greater as the cascade erodes self-coping methodologies²⁸.

SPIRITUALITY

Within the madness of the paradigm of HAE stress response pattern of adaptation is the need for self-soothing of the anxiety and other stressors. It is typical, and for some normal, to attempt this self-soothing within the framework of one's belief system in a higher power. As previously noted, the more severe the life threat and loss of innocence, the stronger one's faith would appear to be clung to in order to provide a safer sense of well-being.

SNOWFLAKE

An Update

Looking back, it seems funny now that I believed I could dedicate a year and find a diagnosis, be treated, and pick up my life where I left off. In reality, that one year led to a diagnosis that will last far beyond my lifetime. Generations of my family both past and future will be able to give the odd symptoms a name... HAE - Hereditary Angioedema.

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