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Quality Assurance and Guidelines Are Necessary to Ensure Adequate Care of Hereditary Angioedema, an Orphan Disease

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ABSTRACT

Background: Hereditary angioedema (HAE) is a life-threatening and disabling genetic disorder caused by a deficiency of C1 esterase inhibitor (C1-INH). Evidence-based recommendations have been established that describe core components of therapeutic management.

Objective: This study assesses the quality of care provided for patients with HAE in a large multidisciplinary clinic compared with care designated by an international consensus of HAE experts.

Methods: Charts were retrospectively reviewed for 60 adult patients with confirmed diagnoses of HAE who received clinical care. The review was performed with data obtained from electronic medical records (EMRs) from the years 2000–2011. Research patients who never received care in the clinic and patients younger than age 18 years were not included. The research met an institutional review board exception.

Results: An acute action plan had been provided to 98% of patients. Medications to avoid were documented in the EMRs in 35% of patients. Of the 60 adults, 58% received fresh frozen plasma at least once, 73% received C1-INH for acute attacks, and 33% received C1-INH for long-term prophylaxis at least one time. For safety evaluation, 48% underwent hepatitis B testing, 42% had hepatitis C testing, and 47% were tested for HIV. Hepatitis B vaccine was administered to 15% of the patients. Of all patients, 43% were taking androgens for long-term prophylaxis and 37% for short-term prophylaxis. In addition, 45% had liver function tests, 40% had a lipid profile, and 30% had an abdominal ultrasound.

Conclusion: Guidelines to recommend appropriate care for patients with HAE are crucial, and quality assurance programs are essential, especially in orphan diseases.

INTRODUCTION

Hereditary angioedema (HAE) is a rare, life-threatening, and disabling genetic disorder caused by a deficiency of C1 esterase inhibitor (C1-INH). Guidelines and evidence-based recommendations have been established that describe core components of therapeutic management.[1] The 2010 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema included the following recommendations to provide optimal care for patients with HAE[1]:

- All patients should have an acute action plan
- All patients should undergo hemovigilance (hepatitis B, hepatitis C, hepatitis G, HIV, human T-cell lymphotropic virus [HTLV], and parvovirus testing) at baseline and yearly thereafter
- All patients should be vaccinated against hepatitis B
- Estrogens, hormone replacement therapy, and angiotensin-converting enzyme (ACE) inhibitors should be avoided
- Laboratory testing for adverse effects of androgens should include urinalysis (UA), complete blood count (CBC), blood urea nitrogen/creatinine (BUN/Cr), lactate dehydrogenase (LDH), creatine kinase (CK), alpha-fetoprotein (AFP), liver function tests (LFTs), and a lipid panel, PT/PTT at diagnosis; then LFTs, lipid panel, CBC, and UA every 6 months; and ultrasound of the liver and spleen and AFP yearly.

The aim of our retrospective study was to compare the care received by patients with HAE in a large multidisciplinary group with the care recommendations published in an international consensus by HAE experts.

METHODS

We conducted a retrospective chart review on 60 patients with confirmed diagnoses of HAE type 1 (HAE with deficient C1-INH) or type 2 (HAE with defective C1-INH) who received care between 2000 and 2011. It should be noted that some of the care was provided prior to the guidelines and thus does not necessarily reflect poor

adherence to, but instead the need for, guidelines. Patients aged ≥18 years were included. The data were obtained from electronic medical records (EMRs), and research patients were excluded unless they also received clinical care. Our study met an institutional review board exception because it was a quality improvement project. These data are descriptive only and not analyzed statistically. An assessment was performed to see what type of care patients were receiving compared with international published guidelines. To emphasize the care assessed may have occurred prior to the establishment of the guidelines, this quality assurance program highlights the need for guidelines and not necessarily the lack of adherence to the guidelines. Furthermore, guidelines published after those that were used for this quality assurance and safety project have not altered on the recommendations assessed.[1-4]

RESULTS

For our quality-of-care assessment, we found 60 eligible adult patients with documented laboratory results to confirm their HAE diagnosis, of whom 68% were female. Of the patients, 70% had a family history of HAE, and 98% were provided with an acute action plan. None of the patients in our study were taking ACE inhibitors. One patient, for whom the benefits outweighed the risks, received estrogen because she had high testosterone and low estrogen levels, with associated ovarian failure. Of note, even with very high doses of C1-INH given as prophylaxis, this patient was unable to continue taking estrogen, owing to the severity and number of her attacks. Medications that should be avoided by patients with HAE (estrogens, hormone replacement therapy, and ACE inhibitors) were documented in the EMR in only 35% of the cases.

In our data set, 58% of the patients received fresh frozen plaza (FFP) and 73% received C1-INH for acute attacks at least once. Of our patients, 33% were taking C1-INH for long-term prophylaxis. Only 29 patients (48%) had hepatitis B testing, 25 (42%) had hepatitis C testing, and 28 (47%) had HIV testing documented in their EMR, despite the use of blood products. Hepatitis B vaccine was advised in only 15% of the patients.

Of the patient population, 43% received androgens for long-term prophylaxis and 37% received androgens for short-term prophylaxis. Only 45% had LFTs performed, 40% had a lipid profile documented, and 30% had an abdominal ultrasound; however, we realize that patients with only short-term prophylaxis with androgens do not require safety laboratory testing. Only 10% had a CBC, UA, BUN/Cr, prothrombin time/partial thromboplastin time (PTT/PT), LDH, CK, and AFP evident in their EMR. The duration between the repeat tests varied from physician to physician, ranging from once every 3 months to once every 2 years.

During the study period, we had 3 deaths in the cohort. An elderly male, treated with high-dose androgens for more than 2 decades despite absence of attacks, died of hepatocellular carcinoma. A middle-aged female died of hepatitis while on high-dose androgens, despite recommendations to change over to C1-INH for prophylaxis. The third patient died of unknown etiology, possibly from upper airway swelling despite having been prescribed specific therapy.

DISCUSSION

We have identified areas of improvement in providing quality care to patients with HAE, based on consensus documents.[1-4]

As with other chronic diseases, a flow sheet to document appropriate care is essential and helps to ensure that recommendations are adhered to (**Figure**). Although orphan diseases are generally not included when developing EMR's, our data suggest that EMRs can be used as a tool to improve the care of patients with rare diseases. This may be more important for rare rather than common diseases, as physician knowledge about rare conditions is often limited. Our data also support that a visit to a HAE specialty clinic at least once a year is appropriate guidance to optimize care.

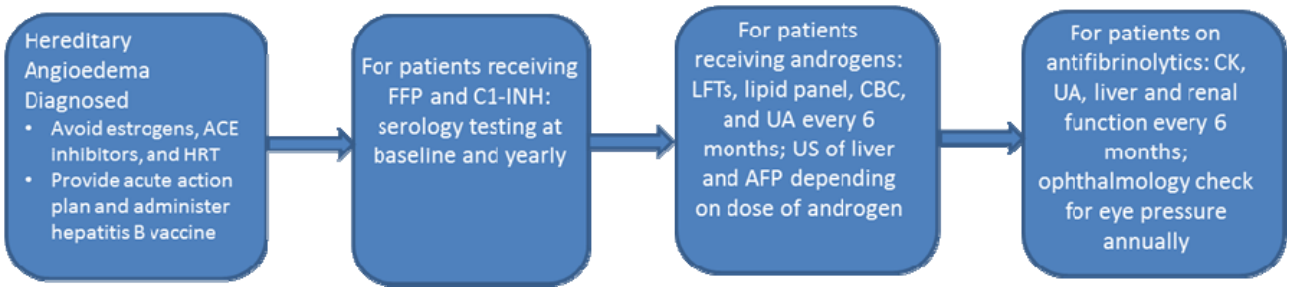

Figure. Checklist for patients with hereditary angioedema (HAE).

ACE, angiotensin-converting enzyme; AFP, alpha-fetoprotein; C1-INH, C1 esterase inhibitor; CBC, complete blood count; CK, creatine kinase; FFP, fresh frozen plasma; HRT, hormone replacement therapy; LFTs, liver function tests;

Because of the risks involved in receiving C1-INH or FFP, all patients should be screened for blood-borne pathogens yearly and be vaccinated against hepatitis A and B. The risk of blood-borne diseases is extremely low because of the screening of blood donors and the multiple steps used in the preparation and production of C1-INH, but it is not zero. Cases of transmission of hepatitis C from C1-INH were reported in Italy in the 1980s, before pasteurization was added to the processing of plasma. Now, pressured heat pasteurization and nanofiltering are both able to remove blood-borne pathogens and no blood-borne diseases have been recorded after instituting these processes. However, human error and machine error can occur, making it possible for virus to be transmitted. Without serial assessment, it is impossible to know if a patient has acquired a blood-borne disease. Moreover, these data are important for postmarketing surveillance programs.

Estrogens and ACE inhibitors should be avoided, and we found that adherence to this recommendation was appropriate. Educating patients to avoid these medications is necessary to decrease morbidity and potential mortality. In addition, designating in the EMR that these drugs should be avoided decreases the likelihood that uneducated healthcare providers will prescribe them.

Adverse effects associated with androgen are hoarseness or deepening of the voice, unnatural hair growth, or unusual hair loss, enlarged clitoris, enlargement of prostate, tumors of the liver, liver cancer, or peliosis hepatis (a form of liver disease) have occurred during long-term, high-dose therapy with androgens. When androgens are used in high doses in males, they interfere with the production of sperm. Because of adverse effects associated with androgen use, laboratory monitoring is essential. Increased monitoring with UA, CBC, and a complete metabolic panel and lipid panel, all every 6 months, as well as an ultrasound every year, appears necessary and may have been underutilized for patients on androgen therapy. As our database made it difficult to distinguish between short- and long-term androgen prophylaxis, and because screening is not necessary for those with only intermittent use of androgens for short-term prophylaxis, we may not have underutilized the safety screening.

We found that the majority of patients with HAE appropriately had a printed acute action plan (**Table**). The action plan included data about their healthcare providers so that patients and physicians can contact them for queries. It also included patient information in case of upper respiratory involvement causing an inability to communicate. Information about symptoms and signs of HAE and about the appropriate medications for HAE was included for the education of healthcare providers, especially emergency department physicians. Lastly, a summary of the therapy the patient is receiving and how to treat him or her for an attack is also included on the acute action plan. In the future, it would be wise to post the action plan online and have the website referenced on the Medic-Alert bracelet or necklace so that the patient does not have to carry the instructions; this also would be useful in an emergency setting.

For the duration of the study, adherence to the guidelines increased secondary, to better education of physicians and new guidelines.[1-4] The quality improvement project began in early 2000 and we compared it to the guidelines published in 2010; thus, we anticipated that there would be many items to improve upon. Our data suggest that guidelines are essential and allow centers to make the necessary steps toward achieving universally accepted standards. A concern is that patients with HAE are increasingly cared for by physicians who may only have 2 or 3 such patients and adherence to recommendations by the physicians may be lacking. This is especially true as we focus on home and self-treatment.[2,5-8] With self-care, the need for visiting the clinic lessens and may predispose to poor quality of care unless there is adherence to annual visits. We suggest that a checklist for HAE and other rare or orphaned diseases be included in the EMR to ensure that optimal and complete care is delivered.

As more therapies for HAE become available, postmarketing surveillance becomes all the more important to assess for effectiveness and adverse effects of treatments, because adverse events may be difficult to determine based on one or two phase 3 studies with a limited number of patients and treatments. Also, periodic reassessment of patients may provide data leading to needed changes in future guidelines for HAE. In addition, quality assurance programs can help determine what education is needed for patients and physicians. Reassessment of care by periodic quality assurance programs is key to optimizing care for all patients.

There are some limitations to our study. First, we used consensus guidelines that are a few years old; however, the items we assessed have not been altered in consensus guidelines since, and all these items have been emphasized in newer guidelines as well.[1-4] Another limitation is that we surveyed data back to a date much earlier than the consensus guidelines we used. However, as noted, we wanted to compare care of HAE in a group practice to those guidelines and examine what is considered optimal care and not necessarily what our adherence to those guidelines were. An ideal study would be to conduct assessments before and after guidelines are implemented to ensure that patient care is improving by adherence to the guidelines.

Table. Acute Action Plan for Hereditary Angioedema (HAE)

HAE Action Plan: Information for Healthcare providers

Hereditary Angioedema (HAE) is a hereditary disease caused by deficiency or dysfunction of a protein called C1 Esterase inhibitor (C1INH) in the body. The lack of this protein leads to recurrent episodes of swelling of different parts of the body. The swelling may be life-threatening if it involves the tongue or upper airways. Patients often present with severe abdominal pain.

Patient information:

Name: _____ Date of Birth: _____

Address: _____

_____

Phone: Home #:_____ Cell #: _____

Emergency Contact/Caregiver: _____ Phone#: _____

Known Drug Allergies: _____

Healthcare Providers

HAE Prescribing Doctor: _____ Phone#:_____ Fax#: _____

Street Address: _____

_____

Maintenance Treatment (if any): _____

_____

Acute Treatment (if done before): _____

_____

Symptoms of an Acute Attack of HAE:

- Feeling of tightness in throat
- Voice Changes
- Swelling in throat
- Face swelling
- Swelling of hands, feet, arms, le
- Nausea/vomiting/diarrhea
- Belly pain/cramping
- Swelling in genital area
- Ring-shaped, non-itchy rash

What to do for an Acute Attack of HAE:

1. The following medications can be given for an acute episode of HAE:

- **BERINERT**: Berinert is a plasma-derived C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients (older than 12 years).
  - ➢ Administer 20 units per kg body weight. Inject at a rate of approximately 4 mL per minute (1000-1500 units IV over 10-15 minutes).

- **KALBITOR**: Kalbitor (Ecallantide) is a kallikrein inhibitor and should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis.
  - ➢ The dose is 30 mg (3 mL), administered subcutaneously in three 10 mg (1 mL) injections. If an attack persists, an additional dose of 30 mg may be administered within a 24 hour period.

FIRAZYR: Firazyr is approved for acute attacks of HAE in adults 18 years and older. Patients may self-administer
- ➢ The dose is 30 mg injected subcutaneously in abdominal wall. Additional injections of 30 mg may be administered at 6 hour intervals if response is inadequate or symptoms recur. Do not exceed 3 injections in 24 hours. Available as 10mg/ml

2. Give supportive treatment: airway management, oxygen, intravenous access; treat hypovolemia, pain and vomiting; strong analgesia may be required for abdominal episodes.
3. THERE IS NO ROLE OF ANTIHISTAMINES, STEROIDS AND EPINEPHRINE IN THE TREATMENT OF ACUTE EPISODES OF HAE.
4. Angiotensin Converting Enzyme (ACE) inhibitors are contraindicated in HAE patients. Extreme caution should be exercised in prescribing oral contraceptives to these patients.

CONCLUSIONS

Guidelines help influence appropriate care of patients and are especially important in the management of rare diseases. In addition, EMR checklists (Figure), acute action plans (Table), and education should be employed to improve care of patients with HAE. Lastly, periodic assessments as outlined in this study are important to identify whether patient needs are being met and whether there is adherence to universally accepted standards of care.

DISCLOSURES

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Conflicts of Interest: Dr. Sabharwal: None. Dr. Craig performs research for Biocryst, CSL Behring, Dyax, Shire, and Pharming. He is on the speakers bureau for CSL Behring, Shire and Dyax, and consults for CSL Behring and Biocryst. Dr. Craig is a member of the Medical Advisory Board for the HAE-A.

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