Supporting Family Testing: Talking to Your Patients about Testing for HAE

HAEi

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Introduction and purpose

This leaflet is one in a series that has been designed to support any conversations that you and your patients may have on testing for hereditary angioedema (HAE) and to help understand the potential benefits of being tested for HAE.

HAE is a rare genetic disorder that is caused by an inherited deficiency or dysfunction of C1-esterase inhibitor (C1-INH).[1]
In HAE, increased bradykinin concentrations are the key mediator[2] in the development of the clinical symptoms, which can include severe abdominal pain, nausea and vomiting,[2] cutaneous swelling affecting the limbs, genitals or face,[1,2] and potentially life-threatening laryngeal swelling,[3] Around half of all HAE patients suffer from at least one laryngeal attack during their lifetime.[1]

The high mortality with undiagnosed HAE underscores the need to identify patients and diagnose their condition as early and accurately as possible.[4]

It is important to stress to patients that you believe may have HAE and who are undergoing testing, that with the right help, support and treatment HAE can be effectively managed[2] to enable people with HAE to have fulfilling and active lives.

HAE identification

The clinical criteria that should prompt any physician to investigate a diagnosis of HAE are:[5,6]

- Recurrent angioedema (without urticaria)
- Onset of symptoms in childhood/adolescence
- Recurrent abdominal pain and vomiting
- Occurrence of upper airway oedema
- Failure to respond to antihistamine, glucocorticoid, or epinephrine
- Prodromal signs and symptoms before swellings
- Family history of angioedema and/or abdominal pain

A patient presenting with these signs and symptoms should undergo laboratory testing to aid in the diagnosis of HAE. As a hereditary disorder, and because the onset of symptoms of HAE can occur at a young age, it is also recommended that the children of families with HAE are tested as early as possible.[7] Investigations carried out in patients before the age of one year should be confirmed after the age of one year as tests may not be reliable in children under one year.[6]

Due to the genetic pattern of HAE, it is important to raise the matter of family history.[6] This information can help confirm a diagnosis.[6] If the patient has experienced HAE in their family – whether diagnosed or undiagnosed – this can be a sensitive issue to discuss. All family and individuals react differently and in previous generations there may have been a very stoic approach to HAE which may have an effect on your patients' attitude.

Talking to your patients about testing

The path to considering a test to diagnose HAE can often be complicated and frustrating for a patient and their family. For those patients without diagnosed family members, it may have taken years to reach this stage and the patient may have experienced a number of misdiagnoses or unnecessary surgery already.[8]

Those patients with diagnosed family members may or may not be exhibiting symptoms and are seeking confirmation of their HAE status. There will also be patients with a confirmed diagnosis seeking more information to encourage their family members to be tested.

Whatever the reason for discussing testing for HAE, making the decision to be tested directly, or on behalf of a child, is

complex and will vary between patients. Many of the common objections, positive reinforcements and questions asked by patients are covered here.

The possibility of a diagnosis of HAE

The possibility of a diagnosis of any condition will raise lots of questions for the patient although they may not always be ready to ask all the questions they have.

When discussing the possibility of a positive result and your patient's feelings and actions around receiving a diagnosis, it can be worth enquiring about other family members who should consider being tested for HAE.

Your patient's willingness to be tested could be influenced by the extent of the symptoms they have been experiencing to date and any wider experiences of HAE in their family. Common reasons why patients or their family may not want to consider testing for HAE could include:

- They may have had mixed or negative experiences of living with HAE [9]
- They may not be interested in knowing or in a form of denial that the condition is in their family [10]
- They are extremely anxious or fearful that a confirmed diagnosis becomes a tangible threat to their life [10]
- They may have a fear of needles or the test itself [11]

There are also patients who have a very positive approach, and want to know and understand their HAE status or the HAE status of their children, to be able to take positive action:

- To make the most informed decisions about their care and treatment [12]
- To be able to plan for any eventuality of an attack their children may have [12]
- To recognise their or their children's specific prodomes and symptoms, to be able to take prompt action [12]
- To demystify the condition and help family members understand what is happening during an attack [12]
- To be empowered with knowledge of HAE and understand their attacks [12]

Practical tips for the discussion

The following recaps key areas that you will be familiar with when approaching any discussion with a patient about a potential diagnosis and or diagnostic test. This covers ideas from conversations with experts that may support you in discussing testing for HAE with your patient.

- Use a combination of open and closed questions to give your patient time to think and answer as openly and honestly as they want to [13]
- Before you raise testing for HAE with your patient, consider the following as they may influence your conversation or come up in the discussion:
    - Your patient's journey to reach this stage and discussing a test [14, 15]
    - Your patient's family history [14]
    - Your patient's age and family situation - do they have children, are they struggling to hold a job down?[9,16]
    - The importance and value of other family members being tested in due course [18]
    - Expert clinics and patient advocacy support available in your area [17]

The test and receiving the results, HAE diagnosis, treatment options available and next steps

How the test for HAE is conducted and how the results are received will vary between hospitals; to help manage the patient's expectation of what the test and process are, these are examples of questions frequently asked by patients about testing for HAE:

- What does the test involve?
- How is the blood taken?
- Will it hurt? Will I need to arrange for someone to take me home afterwards?
- Where does the blood sample go for testing?
- How long will it take for the result to be available?
- How will I receive the results?
- Is there anything I should know about or do when I am waiting for my results?
- What are you looking for?
- What will the test show?
- Will it be absolute confirmation that I have HAE or is there a 'grey area'?

- Should anyone else in my family be tested?
- What are the next steps?

Your patient may well have concerns about the testing method, especially if they are needle-phobic[11].

There are scenarios where patients who have shown signs and symptoms of having HAE have a 'normal' HAE blood test result.[6] If your patient has been experiencing symptoms and is looking for answers and a potential management or treatment plan, this can be hard news to receive. Ensuring all test outcomes are discussed in advance can help prepare patients for all eventualities.

HAE Diagnosis

Laboratory testing (immunohistochemistry) will determine levels of the complement protein C4 and C1-INH antigenic protein and function.[5,6]
In all cases, these tests should be performed on fresh blood plasma, taken when the patient is not being treated for their condition as this may affect the results.[19,20] Tests should be repeated at least once to confirm the diagnosis.[5,6] If C4 and C1-INH antigenic protein are normal despite clinical suspicion of C1-INH deficiency, the test should be repeated during an actual HAE attack.[5,6]

- If levels of C4 and C1-INH antigenic proteins are both low, the diagnosis of HAE Type I can be made. Around 85 percent of patients have Type I HAE, which is the most common form. [6]
- If levels of C4 are normal or low and C1-INH levels are normal but the clinical suspicion is strong, the functional activity of C1-INH should be tested. If this test demonstrates that the activity of C1-INH is low, HAE Type II may be the diagnosis. This is the second most common form of HAE, affecting around 15 percent of patients.[6]
- If C4 levels and C1-INH levels and activity are normal, HAE Types I and II can be ruled out.[6] This does not rule out HAE with normal C1 inhibitor (also known as Type III), nor medication-related angioedema, which should be further investigated.[6] HAE with normal C1-inhibitor is the rarest form, the least understood and mostly affects women.[6] Two subtypes have been described, one linked to mutations in the Factor XII (FXII) gene and the second without FXII mutation.[6,21]

Type of HAE	Cause	C1-INH	% HAE patients affected
Type I HAE	C1-INH gene mutation	Decreased plasma levels of C1-INH, low activity	Around 85%
Type II	C1-INH gene mutation	Decreased activity of C1-INH, plasma levels normal or increased	Around 15%
HAE with normal C1 inhibitor (previously known as Type III)	Cause unknown, though may be exacerbated by oestrogen and in some cases linked to a mutation of the FXII gene[20]	Normal C1-INH levels and activity	Rare (approximately 1% of patients with HAE), occurs mostly in women

If the results confirm HAE, it is important to reassure patients that with the right help, support and treatment it can be effectively managed to enable people with HAE to have fulfilling and active lives.

While there is currently no cure, there are medications licensed for the treatment of HAE which can prevent or help reduce the frequency and severity of attacks, enabling patients and their families to manage their symptoms and lead normal and active lives.

The HAE treatment options focus on two strategies[5,6]:

- Acute treatment
- Prophylactic or preventative treatment

Treatment and management guidelines for HAE as well as access to therapy may vary but the following sources of information may be useful:

Hereditary Angioedema International Working Group guidelines:

Cicardi M, Bork K, Caballero T, Craig T et al on behalf of HAWK (Hereditary Angioedema International Working Group). Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. Allergy 2012; 67: 147–157

Craig T, Pürsün E, Bork K, et al, WAO Guideline for the management of Hereditary Angioedema. WAO Journal 2012; 5 (12): 182-199

If your patient has not yet experienced HAE symptoms, early diagnosis and advice on how to recognise symptoms, should they occur, and what to do if they feel a swelling attack coming may help them respond in the event of a laryngeal attack[4].

A crucial part of talking to your patient about their diagnosis is communicating that HAE is hereditary and may affect other family members[2]. In order to ensure that they also have the best possible care, you should discuss the possibility of family members also being tested.

Your patient is likely to need a variety of support[12] so it may help them if you give them the contact details of the local HAE patient support group. The international support group, HAEi, may also be a source of information for your patients.

In Summary

- HAE is a rare genetic condition[1] which without accurate diagnosis, optimum management and treatment can be debilitating and even fatal[4]
- With the right help, support and treatment, HAE can be successfully managed to enable people living with it to have fulfilling and active lives
- Testing for HAE can provide diagnosis and the stimulus to treat and manage a person's HAE
- Having the discussion about testing for HAE can raise a number of complex issues
- There will be many different reasons that a patient may have concerns about being tested for HAE[10]
- There are benefits to testing[4] that should be communicated to your patient to enable them to make an informed decision
- Your patient may have many questions about being tested for HAE and support is available to enable you to respond, both in the content of this leaflet series and via groups and websites
- Your patient may have questions about the test and testing process before they make the decision go ahead with the test[10]
- Some of the answers they require may be specific to your clinic and geography
- Making the decision to be tested for a disease can raise some complex issues for your patient.[10] Be prepared for any questions that they may have and allow them the opportunity to discuss testing freely
- There are varied treatment options available to your patients[5,6] but it is dependent on each individual situation and the arrangements in your locality[12]
- As well as discussing a disease management plan with your patient you should also address the matter of other family members who might also benefit from being tested[6]
- At every stage of these conversations, it is important to remember that with a proper understanding of the condition and the different treatment options, HAE patients and their families may be able to manage their symptoms[12,15] and lead normal and active lives.

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HAEi