

Consider Rare: Suspecting and Diagnosing HAE

Dr. Jonathan Bernstein:

Hello, I'm Dr. Jonathan Bernstein, I'm Professor of Medicine at the University of Cincinnati in the Department of Internal Medicine, Division of Immunology in the Allergy Section and a Partner Advanced Allergy Services in the Bernstein Clinical Research Center in Cincinnati, Ohio.

And today, we're going to talk about a rare condition called Hereditary Angioedema, and the title of this talk is: Suspecting and Diagnosing Hereditary Angioedema. This is a program that is being supported as a CME program, and this information is outlined here and the specifics related to financial relationships are cited. HAE is a rare genetic disorder that leads to recurrent and unpredictable episodes of angioedema. Airway swelling can be life-threatening when it affects the larynx, and it can certainly have a significant impact on quality of life. Significant improvement over the past 15 years for treating both acute and attacks and preventing attacks has been made with the development of some very novel therapies.

When we look at the diagnosis, we can see that the gene's effective is the SERPING1, and there are three types of HAE conditions. HAE-I, which makes up 85% of cases is resulting when there is a low functional activity of C1 inhibitor, but also a low level of C1 inhibitor. So in this case, they just don't make the C1 inhibitor, it's just the C1 inhibitor is not made. And the HAE-2, which is 15% of cases, we typically associate it with a normal C1 inhibitor antigenic level but has also a low functional level. In fact, sometimes the C1 inhibitor antigenic level can be high, but both of these conditions, both type I and type II have low C1 inhibitor functional levels and they both affect the gene, in one situation, it doesn't make the protein, in the other situation it makes it but it doesn't work.

Now there's a third type called normal C1 inhibitor deficiency, and it used to be referred to as type III, but the correct terminology is normal C1 inhibitor. And there are several mutations that have been associated with this condition, including factor XII mutation, plasminogen, angiotensin, kininogen, myoferlin, heparin, and there are probably many other unknown genes. However, the vast majority of these cases we have not been able to identify a genetic mutation and therefore it's difficult to diagnose these patients. The mechanisms are still poorly understood, but it's likely believed to be due to activation of the contact system where there's increased bradykinin activity or increased susceptibility to vascular leak.

And this is a nice slide that shows that pathophysiology of Hereditary Angioedema, and you can see that it integrates the complement system on the far left, the contact system in the middle, and then the plasminogen pathway. And what you can see is that C1 inhibitor is critical for regulating many of these processes and it actually promotes the breakdown of Prekallikrein or the conversion of Prekallikrein to kallikrein. It also can regulate Factor XIIa activation, and again, it also has an effect on plasminogen as well as on the complement system. And this is a very simplistic overview, and you can see where C1 inhibitor can have an effect not just on the bradykinin pathway but also on these mutations that are associated with normal C1 inhibitor.

Now this is a timeline of HAE prophylaxis and on-demand treatment, and we can see that prior to 2008 was when C1 inhibitor, plasma-derived C1 inhibitor, was introduced into the formularies in the United States. All those patients had been on danazol for preventing attacks and fresh frozen plasma which was used during acute attacks. So the treatments were significantly inadequate. With the advent of intravenous C1 inhibitor, which is replacement C1 inhibitor, patients were able to have a treatment that reduced attacks, and when they used it regularly, could prevent attacks, although it only really prevented about 50% of the attacks and it's likely due to the fact that this was a set dose and was not a weight-based dose. In 2009, we had on-demand therapies, both ecallantide, which is a plasma kallikrein, inhibitor and also Berinert, which again is a plasma-derived C1 inhibitor replacement therapy. In this

situation, Berinert was weight-based, 20 units per kilogram, and so it was found to be very effective in preventing the progression of an acute attack.

Ecallantide was also effective, but during clinical trials, it was reported that patients could have allergic reactions and therefore it received the box warning from the FDA and could not be self-administered without the presence of a healthcare professional. And it was in 2011 where Icatibant was released to the market and this was a bradykinin 2 receptor antagonist that was given subcutaneously and was very effective in preventing progression of acute attacks. However, this had, and this could be easily carried around with the patient, but this treatment although effective, was associated with localized pain and discomfort at the injection site. In 2014, Ruconest, which was a recombinant C1 inhibitor replacement therapy, and this is a light Berinert, it is a C1 inhibitor molecule but it's derived from rabbit breast milk, and so there's an unlimited supply of this on-demand treatment that is effective in controlling acute attacks from progressing.

And then we developed, in 2017, we had HAEGARDA, which was a C1 inhibitor, but this was given subcutaneously and it could actually be used prophylactically every three to four days to prevent attacks. And this was followed by Lanadelumab, which again was a kallikrein inhibitor which was given subcutaneously and was initially given every two weeks, so it had a longer half-life and then after six months if there was no attacks it could be spread out to every four weeks. And lastly, Berotralstat, which was the first oral kallikrein inhibitor, and this was shown to be very effective, it completely prevented attacks in 45% of patients who took it, but many who took it still had breakthrough attacks. So all of these therapies, while they were great advances in improving the quality of life, reducing attacks, allowing patients to treat acute attacks promptly, they still were breakthrough attacks and there were still significant impairment in terms of portability, in terms of the way it was administered and such, and the half-life, the frequency of use.

So we now have in development other treatments like Garadacimab, which is a factor-XIIa inhibitor, we have Donidalorsen, which is again another kallikrein inhibitor but it works so by blocking prekallikrein. And now we also have Deucritibant, which is a bradykinin 2 receptor blocker, an oral agent that will be developed both for prophylactic use as well as for on-demand use. And finally, Sebetralstat, which is another plasma kallikrein inhibitor which is being developed as an on-demand oral therapy. So a lot has been accomplished in the last 15 to 20 years. Now diagnostic delays are very common with HAE. It's estimated that a delay of up to five to 15 years is common, especially when patients are seen by individuals who are less experienced with evaluation and diagnosis of this rare condition. Therefore, awareness of HAE in the medical community is essential, and it has improved the diagnosis time, but only one third of HAE patients are still diagnosed within the first year, and this is usually because of a family member being diagnosed, so it's somewhat easy, but if there is no clear family history, which can occur in up to 25% of patients, they can be overlooked.

Common misdiagnoses, especially when patients present with abdominal pain, is appendicitis, but also allergies or mental disorders. In fact, we used to call Hereditary Angioedema, hereditary angioneurotic edema before they knew what the cause was, but once we identified that there was a defect in the C1 inhibitor gene, that terminology was changed to HAE. But also tonsillitis, especially where patients are complaining of throat swelling, or patients just being told we have a nervous stomach they're having, this is the reason why they're having all these recurrent abdominal attacks.

So let's have a reflective question. What are the benefits of an early diagnosis of HAE? Well, the benefits are to reduce unnecessary patient discomfort, it actually can help to reduce unnecessary doctor appointments and unnecessary medical procedures, it also reduces loss of work, and it allows patients to receive properly targeted therapy for their condition. So let's turn to suspecting HAE. What are the onset of symptoms? So symptoms of HAE typically begin in childhood and worsen during puberty.

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There's a family history of HAE. As I mentioned, in 75% of cases, 25% have no known family history and may have a de novo mutation that subsequently follows an autosomal dominant inheritance pattern. But in general, the patients who have this condition, it is an autosomal dominant pattern with variable penetrates, and this nice pie diagram shows the breakdown. Whereas 85% are type I and there's an even distribution between males and females, about 15% are type II again an even distribution between males and females.

A much lower number of patients have been diagnosed with normal cellular inhibitor, and we still don't really have good epidemiologic data on this condition at the present time. There's a wide range of symptoms associated with HAE. When patients have increased Bradykinin production, which is a potent vasodilator. There is fluid extravasation that goes into the deep dermis, the subcutaneous tissue, and the submucosal tissue, and this leads to very severe swelling. As you can see on the pictures on the right, and affects the skin and mucosal surfaces, but any skin location can be affected including the hands, the face, the feet, the genitals. It's not accompanied by urticaria or itching, so this is very important. Whereas mast cell-derived angioedema can be associated with hives in up to 40% of cases, this condition is not, and there can be a prodrome associated with this condition. One of the more common ones is a non-itchy rash called erythema marginatum, and this is seen in up to 30% of patients, although this number varies depending on the population study.

And you can see on the right, this very faint rash which has serpiginous borders that can show up before the onset of the attack. Depending on the location of the attack, episodes can be very disabling, and if it's affecting the throat, it can be potentially life-threatening. Up to 50% of patients might have a throat swallow instance episode at some point in their life and this is the most ominous attack because it can lead to asphyxiation if it's not recognized and treated early. The GI tract though is a very common area to be affected, it leads to very severe abdominal pain, nausea and vomiting. This is showing a more updated and a closer picture of the serpiginous rash, in this case on the individual's forearms, their abdomen, and their hand.

So what are the triggers and patterns of attacks for HAE? Well, many episodes do not have a known trigger, however, common triggers of HAE attacks can include emotional or physical stress, minor trauma, surgical procedures, infections, ACE inhibitors, which are contraindicated in patients with HAE, and changes in estrogen levels. The episodes of HAE attacks are variable. The frequency can occur every week to once a year. Many untreated patients have attacks, however, every one to two weeks and most untreated attacks can last two to four days if they don't get treated. Swelling can occur in one or multiple parts of the body during an attack, and the location and frequency of the swelling will vary widely within as well as among individuals. It can occur from several times a week to less than once a year as I've mentioned.

So what is the reason why there's delayed diagnosis? Is it because patients live in rural communities where they don't have immediate access to experts who know how to diagnose and manage HAE? Is it due to race or ethnic inequalities? Data's limited in this area, but there is a concern as to why this is occurring. Here's a geographical map showing that one-fifth of HAE patients actually live in rural areas where they're not close to a medical facility where there are HAE experts. It's very important therefore that we establish angioedema centers of excellence around the country to help these individuals access individuals or doctors who know how to diagnose and manage this rare condition. Now this is an interesting real world study, a study comparing real-world HAE, just ethnicity and distribution compared to clinical trials, and you can see that there's an over-representation of both white and Asian patients and an under-representation of Black patients and Hispanic patients in clinical trials. The sex distribution of patients however, is not different between real-life data and clinical trial data. So it does tell us that

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there is a limitation in terms of having this diversity in the different populations within the different areas of the country.

So diagnosis of HAE, Let's have another self-reflective question. Are you aware of best practices to diagnose HAE? Well, these are summarizing some of the best practices. First of all, there needs to be recognition of symptoms, it's critical for correct treatment. The common symptoms, as I mentioned, are recurrent subcutaneous edema without urticaria, there's abdominal symptoms in many situations, and less commonly there be upper airway symptoms. A clinical test that one would order is a C4. If someone comes in and has no family history and has isolated angioedema, this might be a sufficient screening test. If there's a high suspicion for Hereditary Angioedema, then getting a C1 inhibitor functional level as well as an antigenic level would be appropriate.

In some cases, these tests can be equivocal, they may not be definitive depending on the age of the patient, certainly if they're babies, you might see false negatives, and sometimes genetic testing is normal to look at the SERPINE1 gene to see if there is a mutation. In the case of normal C1 inhibitor, we definitely need to get genetic testing to see if they do have one of the common mutations like factor XIIa or plasminogen, or angiopoietin. But these tests are somewhat difficult to obtain, but they can be performed in commercial laboratories. Screening should also be performed on all first-degree relatives to see if there are undiagnosed cases of Hereditary Angioedema in these families.

This is a table that summarizes the lab tests, and what we briefly mentioned earlier is that for HAE-I, where there's a defect in the gene that prevents patients from producing this protein. These individuals have low C4 levels and they have low antigenic levels, as well as low functional levels, and you rarely need genetic sequencing because of these tests that correlate with their history. And for HAE-2, these individuals also have low C4 but they have a normal to elevated antigenic levels, I've mentioned, and also a low functional level. And again, genetic testing is rarely needed for these patients based on their lab testing. Now in the normal C1 inhibitor, not surprisingly, these patients have normal C4, normal antigenic levels, as well as normal functional levels. In these situations, some limited genetic testing if these mutations are available might be useful, but mind you, not all of these mutations have been identified. And laboratory results must always be interpreted in conjunction with the patient's history.

So this is looking at the different tests that are ordered and in HAE-1, all of the patients have decreased C4, C1 inhibitor, quantitative and functional levels. Now in patients, some patients may actually present later in life, so after the age of 30, and may have no family history, but they still have the same symptoms and the same lab tests. It would be important to get a C1q level. And if that's low, which can occur in 70% of cases, it's very likely these patients have something called acquired angioedema, and this is a form of angioedema where patients either make an autoantibody against C1 inhibitor, which inactivates it and makes it sort of doesn't function properly, or they have some type of lymphoproliferative disorder like a Monoclonal gammopathy of unnerving significance which can consume complement. And so this is a much rarer condition. Whereas Hereditary Angioedema might be in one in 50,000, this condition is one in 500,000.

The HAE-2 again is C4, the C1 inhibitor function is low, but the C1 inhibitor quantitative level is normal or actually even elevated. And we can see that if it's all normal and there's a family history or in a causative mutation for the normal C1 inhibitor, then this would be definitive a normal C1 inhibitor. If the family history is negative and there's no mutation, then it's more likely the patients might have a mast cell mediated condition, but one could also have idiopathic angioedema or hopefully they're not taking an ACE inhibitor, that would be something that would be a drug induced form of angioedema. Stopping the ACE inhibitor is essential.

Are there additional assessment tools? Well, there's been many studies which have looked at ways of stimulating kallikrein activity, developing assays that would distinguish bradykinin mediated from

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histamine mediated angioedema, so there have been attempts to make a stimulated kallikrein assay. There's a small fragment SPG 120 fragment assay which stands for serum glycoprotein, and then there's also a cleaved high molecular weight kininogen assay that has been worked on. And all of these are meant to look at the actual activity of the kallikrein pathway, which is critical for producing bradykinin that can bind to bradykinin receptors, bradykinin 2 receptors specifically for HAE that leads to swelling.

So what kind of further assessment of follow-up is necessary? Well, if your testing is equivocal and it's not clear, and sometimes it happens in the first year of life, then genetic testing would be necessary. If they are suspected to have HAE normal complement, then one would also get some testing. As we've talked about, it's important to create a multidisciplinary team if these patients have other comorbid conditions, but generally speaking, an HAE specialist should be able to manage these patients quite well. Of course, setting up a management strategy tailored to the patient is essential. So these are some clinical pearls that we can end with. Diagnostic delays are the norm for HAE and we need to do a better job in recognizing this condition and screening these patients for Hereditary Angioedema. Early signs and symptoms as well as family history should trigger the need for diagnostic testing. Diagnosis is fairly straightforward and can provide patient with a management plan that will treat HAE more efficiently and safely. Thank you very much.