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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Identifying the Zebras: Key Insights on Chronic Abdominal Pain in HAE

Dr. Buch:
Diagnosing the source of chronic abdominal pain can be challenging. When investigating the cause of this pain, should clinicians be considering hereditary angioedema?

You're listening to *GI Insights* on ReachMD. I'm your host, Dr. Peter Buch. And today we're joined by returning guest, Dr. Kyle Staller, to explore hereditary angioedema in the differential diagnosis of recurring abdominal pain. Dr. Staller is an assistant professor and the director of the Gastrointestinal Motility Laboratory at Mass General.

Dr. Staller:
Dr. Buch, thanks so much for having me. It's really a pleasure to talk about something really that many of us will not see very commonly, but when we do see it and recognize it, we can make a huge difference in our patients' lives.

Dr. Buch:
Amen. Dr. Staller, let's start with some background of hereditary angioedema, or HAE for short. What are some of the clinical presentations of typical hereditary angioedema?

Dr. Staller:
The typical manifestation that we think the most about is airway swelling, or angioedema, and angioedema is really a leakage from vessels where fluid from vessels leaks out into tissue and causes swelling. But actually, surprisingly, a very common manifestation of angioedema, and hereditary angioedema as well, is actually abdominal pain. And most patients will have some degree of abdominal pain, and some patients will actually only have abdominal pain when they have their attack. So this is something to keep in mind.

Dr. Buch:
Now, focusing in on the GI tract in particular, can you tell us about the barriers that may prevent an HAE diagnosis? And what are the consequences of these delays?

Dr. Staller:
I think the big barrier here is that the GI tract really only has a few ways of expressing displeasure, and of course, one of those is abdominal pain. And the differential diagnosis for abdominal pain is really quite broad, but this specific type of abdominal pain is really in the intermittent abdominal pain category. And I actually love these diagnoses. I keep a list of them on my phone because they're the kind of zebras that do sneak into your clinic under the guise of something like IBS, something like GERD, and I think in general, I would say many of these patients get labeled incorrectly as IBS because IBS also creates intermittent abdominal pain. And so, when we see patients with intermittent abdominal pain, particularly those patients where they have these long periods of quiescence between abdominal pain and they don't have symptoms, which we would expect an IBS person to have, we should start to think about some of these zebras. And because many of us are not seeing these zebras regularly and we may not be attuned to look for them, there's often a very long diagnostic delay between when these patients are seen in various clinical settings and when they actually get a formal diagnosis of hereditary angioedema, and that's one of the reasons why patients' quality of life can really suffer because they're suffering when these types of diseases or this type of disease they're potentially getting treatments that are targeted toward IBS, which is much more common, but they're not seeing that benefit. And of course, some of this can be life-threatening because angioedema, unlike IBS, can actually cause airway swelling, and if that's not recognized as angioedema, that's something that certainly can be dangerous.

Dr. Buch:
And just moving on from there, what are some of the lab tests that may help us make the diagnosis?

Dr. Staller:
I think it's relatively simple. And of course, unless you're an allergist or an immunologist who may be treating these patients directly, which I'm going to assume that most people listening are not, really making the diagnosis here is the most important. It's not necessarily knowing what to treat with and when. It's to make that diagnosis. And it can be relatively easily made with a series of blood tests, specifically C4 for complement as well as the C1 inhibitor assays, both the quantitative assay, how much of that is there, and the functional assay, how much is it working. And these generally will all be decreased in the setting of angioedema whether someone is having an acute attack or not.

Dr. Buch:
Can we assume that CRP during an attack will also be elevated?

Dr. Staller:
It's certainly possible, but this isn't necessarily an inflammatory condition in the traditional sense. You know, I think when we think of CRP being elevated, we may think of things like inflammatory bowel disease. If we're thinking of some of the zebras causing intermittent abdominal pain, an elevated CRP would be much more into the bucket of something like familial Mediterranean fever. But with hereditary angioedema, I don't think CRP would necessarily be there. And I think importantly, you know, you have a very brief window to capture these patients when they're symptomatic. So when someone has abdominal pain with hereditary angioedema, we're probably looking at about 12 to 24 hours of symptoms, and so in general, you would expect that you're not going to be able to capture those patients at that very moment, which is where some of these complement studies and the C1 inhibitor studies can be useful because they're abnormal even in the abscess of an attack.

Dr. Buch:
Thank you for that useful information. For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Kyle Staller about hereditary angioedema as a source of abdominal pain.

So, Dr. Staller, let's switch gears and focus on HAE patients with abdominal pain. Are there any imaging findings we can expect to see for these patients? And what is the sensitivity of these tests?

Dr. Staller:
So, imaging-wise, I think classically we think of someone with submucosal edema in the GI tract, and that can create a variety of findings, primarily on cross-sectional imaging like a CT scan, but as I mentioned or alluded to before, we have a relatively brief window where we will see patients that may have these sort of frank episodes that look classic for edema, and then at that point your radiology colleagues may actually say, you know, this could be consistent with something like angioedema.

If you happen to capture someone after an attack, you may see some ascites in the abdomen, which can be relatively nonspecific, but the majority of patients who get imaging and are not in the midst of an attack may actually have normal findings. And so we really don't know the sensitivity and specificity of imaging because we don't know when the imaging occurs. Is it occurring during an attack? After an attack? But it's not something that I would rely upon to confidently make this diagnosis. We need to rely on our history-taking skills.

Dr. Buch:
Now, why do we need to be especially aware of ACE inhibitors? And what other medications may be implicated?

Dr. Staller:
So there's different types of angioedema. We talk primarily about hereditary angioedema, and these are patients who are diagnosed often in their teens, maybe in their 20s, because this is a mutation and a specific gene that encodes the C1 inhibitor. However, there's also acquired angioedema, and this is almost in some degrees like a paraneoplastic type disorder that happens with lymphoproliferative diseases. And then we have sort of drug-induced angioedema, and this is where the mechanism of the drug in some way influences the same pathways that's implicated in angioedema. And so the classic patient is someone who's on an ACE inhibitor. And, of course, by merely stopping the ACE inhibitor, something like captopril, we can actually improve symptoms. Other medications that are relevant for drug-induced angioedema are NSAIDs for different mechanistic reasons. But NSAIDs could also be a culprit here. And I'd like to mention oral contraceptive agents that contain estrogen. Interestingly, I mentioned that angioedema may often be misdiagnosed as IBS, and of course, IBS is predominantly a female disease. It's occurring in younger individuals, and it may be exacerbated around times of people's menses and other events like menopause.

Well, interestingly, angioedema has a very similar characteristic. We may see more female patients because there is an estrogen sensitivity to attacks, and so patients who are initiated on estrogen containing OCPs may be at risk for having worsening symptoms. People who are having menstrual cycles may be at risk. These types of hormonal changes can also play a role here.

Dr. Buch:

With all this in mind, what are the current recommended treatments for HAE?

Dr. Staller:
The first thing I would say is that if you're not someone who's going to be treating HAE regularly, this is not something that you need to bite off on your own. So, for me as a gastroenterologist, I think my key role here is recognizing someone who could have HAE, having that higher index of suspicion, and then ordering those labs: the C4 level, the C1 inhibitor functional, and quantitative levels that then tell us that this is someone who may have angioedema.

In those cases, that's really where you want to refer to someone who has specialized treatment knowledge. And some of the treatments that are out there are really in sort of two forms. One are sort of abortive treatments where if someone is having an acute attack that could potentially compromise their airway because of airway swelling, and you can use C1 inhibitor concentrations in that setting, but there are prophylactic treatments as well, which are also generally derived from the plasma that are C1 inhibitors as well that have more of a prophylactic role.

But the idea is that you shouldn't have to be navigating this on your own. I think by making the diagnosis, being suspicious of the diagnosis, you really have helped the patient, and then you can get them to the right person rather than trying to do this on your own.

Dr. Buch:
And before we close, are there any takeaways you'd like to share with our audience?

Dr. Staller:
You know, as I alluded to earlier, I think finding these zebras that are mixed in among your classic IBS patients is one of the most fun things that I do in my clinical practice, and so I like to think about what are the types of intermittent abdominal pain type issues or diagnoses that we might see in clinical practice. And so, along with hereditary angioedema, you can think of porphyria, you can think of cyclic vomiting syndrome, you can think of familial Mediterranean fever. These are some of the zebras that can be out there. And so, if something doesn't meet the classic Rome IV criteria for IBS, you should ask yourself 'Does this patient potentially have something else?' And if they do have something else, what are some simple ways like blood tests to be able to distinguish this something else, this zebra, from the more classic IBS?

So just be on the lookout. And when you're on the lookout, you'll make this diagnosis every now and then. And when you do make this diagnosis, that patient's life can be changed immeasurably.

Dr. Buch:
With those interesting thoughts in mind, I want to thank my guest, Dr. Kyle Staller, for sharing his insights on abdominal pain in hereditary angioedema.
Dr. Staller, thanks so much for joining us today.

Dr. Staller:
Thanks so much for having me, Dr. Buch. I appreciate it.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GIInsights where you can be Part of the Knowledge. Thanks for listening, and see you next time.