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Unexplained Chronic Cough—Not Just a Disease Symptom, but a Condition unto Itself

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Unexplained Chronic Cough—Not Just a Disease Symptom, but a Condition unto Itself” is provided by Prova Education and is supported by an independent educational grant from Merck.

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Dr. Dicpinigaitis:
The anatomy and neurophysiology of chronic cough are very complex topics. The abundance of research in this area serves as a solid foundation for the treatment and management of refractory or unexplained chronic cough. Are you utilizing these resources to help improve outcomes in your patients?

This is CME on ReachMD, and I’m Dr. Peter Dicpinigaitis.

Dr. Canning:
And I’m Dr. Brendan Canning.

Dr. Dicpinigaitis:
Let’s get started. Dr. Canning, could you please provide us with a brief overview of refractory or unexplained chronic cough?

Dr. Canning:
Cough, as you know, Peter, is the most common presenting symptom amongst patients seeking medical advice from their primary care providers. When we think of chronic cough, we’re thinking of a cough that persists for 8 weeks or more. Such a chronic cough can be associated with very common conditions, things like asthma and gastroesophageal reflux disease and upper airway conditions, things like rhinosinusitis. When we’re talking specifically about refractory or unexplained chronic cough, we’re talking about a cough that persists despite aggressive medical therapy for all identified underlying etiologies. And this will represent a subset of those patients that will present clinically with chronic cough.

In terms of the epidemiology of chronic cough, it’s quite unique amongst chronic respiratory diseases. There are two aspects in particular that stand out. First, a disproportionate number of patients that present clinically with refractory chronic cough will be women. About 60%-70% of patients that will be diagnosed with a refractory unexplained chronic cough will be women. The other aspect, which is somewhat unique amongst chronic respiratory illnesses, is that the emergence of this disease typically happens in the sixth or seventh decade of life. So patients in their 50s and 60s will present clinically for the first time with a chronic refractory cough.

Dr. Dicpinigaitis:
The other interesting part of the epidemiology, Brendan, is that most patients seeking help for chronic cough, in fact, are lifetime nonsmokers. And you made a very important point that, you know, a physician shouldn’t give the term or diagnosis of a refractory chronic cough to a patient until they’ve really looked for and empirically treated these reversible causes of chronic cough like upper airway cough syndrome, asthma, and GERD.

Dr. Canning:
That is an important point, Peter. I think one of the things that has emerged as we try to understand the pathophysiology of chronic cough is that it is natural for us to think of very obvious causes, things like smoking, and quite often, as you know, many of these patients will have been lifelong nonsmokers, and yet they are coughing excessively, up to the point that their quality of life is greatly diminished.

Dr. Dicpinigaitis:
Right, that's exactly right. Dr. Canning let's dive a little deeper into this. I know you've done an abundance of research on this next topic, which is the anatomy and neurophysiology of cough. Can you please give our audience some insights into the mechanisms of cough?

Dr. Canning:
Cough, as we know, is a vagal reflex. It results from the activation of sensory nerves that innervate the airway's mucosa. Cough is obviously an important – a very defensive reflex. It serves to protect the airways from inhaled irritants or accumulated secretions.

The sensory nerve subtypes that we think play a primary role in transducing cough from the airway's mucosa are of two types. There are A-delta fibers. These are sensory nerves that conduct action potentials in a modestly fast 5 m/s rate. They're thinly myelinated. They terminate primarily in the conducting airways, and they're very sensitive to mechanical stimuli – things that you might anticipate would happen with accumulated secretions or aspiration of food content. They're also very sensitive to acidification of the airway's mucosa. And so when we think of these A-delta fibers, we typically think of them as regulating the important defensive function of cough that we would associate with aspiration of gastric contents or perhaps accumulated secretions.

The second sensory nerve subtype, which we associate with initiation of cough, are the unmyelinated C-fibers. These are relatively insensitive to mechanical stimuli but respond to many of the inflammatory mediators that we would associate with chronic diseases of the airways. And these C-fibers, we think, are the likely regulators of the coughing that manifests in chronic refractory cough.

Dr. Dicpinigaitis:
So Brendan, you gave us some nice insight into the mechanism of cough, and you mentioned how stimuli such as exposure to cold air or strong smells can make a patient with chronic cough start coughing predictably. But everyone's exposed to cold air and strong smells and spicy foods or whatnot, and they don't cough. Why is it that this group of refractory chronic coughers that we see in the office – why do they cough from these very common stimuli?

Dr. Canning:
So one of the concepts that has emerged in cough research is the idea of a cough hypersensitivity syndrome. And there are a couple things that we think about that would manifest that would result in cough hypersensitivity. The first thing that we would think of is that there is an excessive production of stimuli for initiating coughing. So perhaps there's an accumulation of a protussive autacoid – something like bradykinin or ATP – that would form in the airways and drive cough, as alarmins, or as part of an inflammatory process. Secondly, we often think of the sensory nerves becoming hyperexcitable. And there are a couple of mechanisms by which this could happen. Sensory nerves express many different receptors and ion channels on their peripheral terminals, and the expression of these receptors and ion channels can change with disease. There are neurotrophic factors that can change the actual innervation that terminates in the mucosa and the excitability of those sensory nerves. So these are two of the main processes that we think of in terms of peripheral mechanisms for cough hypersensitivity.

In addition to that though, there are potential central mechanisms by which cough can become hyperexcitable. And so one of the unique aspects of cough as a reflex is that there is a tremendous amount of integration of sensory input which finally results in the coughing. And this all happens in the central nervous system. So prior to the initiation of coughing, patients will report an urge to cough in response to some tussive stimuli. And that tells us, neurophysiologically, that the brain is interpreting all this sensory information and then coding the appropriate response. And it's possible that in chronic refractory cough, some of these central regulatory mechanisms – either promoting cough or inhibiting cough – may be altered, such that for any given tussive stimulus, a patient with chronic refractory cough will cough excessively, whereas an otherwise healthy patient will have little or no coughing in response to the stimulus.

Dr. Dicpinigaitis:
For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Peter Dicpinigaitis, and here with me today is Dr. Brendan Canning. We're discussing the anatomy and neurophysiology of refractory or unexplained cough.

So continuing with this topic, Brendan, could you discuss the central regulation of cough?

Dr. Canning:
The vagal sensory nerves which regulate coughing will have their central terminations in the brain stem, and this information arising via

action potentials in these sensory nerves will impinge upon relay neurons in the brain stem, and the communication between these neurons, both the sensory neurons and then their primary relay neurons in the brain stem, will utilize neurotransmitters, things like glutamate and perhaps neuropeptides like substance P and neurokinin A. And they will encode, then, the reflex in the most simplest forms. So cough is actually a remarkably primitive reflex in many ways. Not many components to it. There's a sensory input, a set of relay neurons, and then that then communicates to the motor output which we all recognize as the physical aspects of cough through respiratory muscles.

In addition to that, though, cough is somewhat unique in that we have a tremendous amount of descending control. This can be by either excitatory – so we can cough voluntarily if we have the urge to cough. Some – rarely, patients will have a nervous tic in which they'll cough just spontaneously in response to no stimulus. But there's also a tremendous amount of descending inhibitory control, and we all know this, of course, when we're in social settings that would discourage coughing. So we have the capacity to suppress our cough through a central descending pathway arising from the cortex. And both of these elements likely play important roles in how cough presents in patients.

Dr. Dicpinigaitis:
So Brendan, I found very interesting your comments about the central descending inhibitory control of cough, because, you know, it's remarkable that patients come from great distances to see me at the Cough Center because of their terrible chronic cough, and they then are sometimes frustrated that for the entire 45-minute visit, they haven't coughed at all. Not to mention patients very commonly with chronic cough – not so with acute, but with a chronic cough – a patient will cough literally every waking minute of the day, but when they fall asleep, they will very commonly report six or seven hours of completely uninterrupted sleep. Then they wake up and then the coughing begins. So it is fascinating, this lung-to-brain interface.

And to wrap up the discussion, let's talk about how anatomic and neurophysiologic processes provide a rationale for a targeted and systematic approach to treatment.

Dr. Canning:
So this has probably been the area of research that has contributed most to our more recent breakthroughs in understanding the pathophysiology of cough and also gaining insight into potential therapeutic strategies. I think one of the most important things that has emerged from this work has been the identification of rational therapeutic targets that are expressed on the peripheral terminals of sensory nerves, and particularly those bronchopulmonary C-fibers. There are a number of different ion channels that have shown great promise. There are autacoids, things like ATP and bradykinin, which have specific receptors on the sensory nerves which provide the rationale for developing new therapies. And as we've seen over the past 10 years, many of these promising therapeutics have resulted in very encouraging clinical results with drugs targeting those specific receptors and ion channels.

Dr. Dicpinigaitis:
Certainly as a clinician on the sidelines treating patients with cough, it's been so satisfying for me to see in the last 10 years that our enhanced knowledge of the pharmacology and neurophysiology of cough has led directly to a number of drugs in the pipeline that are eagerly awaited, certainly by all of us.

So this has certainly been a fascinating conversation, but before we conclude, Dr. Canning, can you share with our audience your one take-home message?

Dr. Canning:
I think one of the most satisfying things as a cough researcher over the past 10 years has been the ability to provide a clear rationale for both the emergence of chronic cough as a condition and as a disease in and of itself, but furthermore, the ability to provide a rational therapeutic strategy based on sound science performed at the nerve ending level and at molecular level, and I think these sorts of breakthroughs have really made cough research both exciting and, I think, quite productive over the past 10 years.

Dr. Dicpinigaitis:
Absolutely. And I'll just add my clinician's point of view that we are awaiting drugs for refractory chronic cough, but I will continue to make the point that it's the physician's job to make sure that we do a very thorough evaluation for reversible and treatable causes of chronic cough before we then go on and render a diagnosis of refractory or unexplained cough.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank you, Dr. Canning, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Canning:
Thank you, Peter.

Announcer:
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