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Identifying the Respiratory Manifestations of TK2d: The Pulmonologist's Role

Announcer:
You're listening to *NeuroFrontiers* on ReachMD, and this episode is supported by UCB. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is *NeuroFrontiers* on ReachMD, and I'm Dr. Charles Turck. Joining me to talk about the role of pulmonologists in identifying respiratory manifestations of thymidine kinase 2 deficiency, or TK2d for short, is Dr. Bethany Lussier. She's an Associate Professor of Internal Medicine at UT Southwestern Medical Center in Dallas, where she's also a member of the Division of Pulmonary and Critical Care Medicine. Dr. Lussier, thanks for being here today.

Dr. Lussier:
Thank you so much for having me.

Dr. Turck:
Well, to start us off, Dr. Lussier, let's say a patient presents with respiratory symptoms that don't quite align with typical pulmonary findings. What clues would raise your suspicion that something beyond primary lung disease might be driving their condition?

Dr. Lussier:
We get a lot of these patients who come in with extreme dyspnea and no answers. It's an unfortunately common thing that we encounter in the pulmonary office. I think one of the things that guides us most towards a deeper dive into the symptoms to try to find a different diagnosis is when somebody's symptoms and their imaging findings don't align. So somebody comes in with severe or extreme dyspnea, and their imaging may be completely normal, right? Sometimes the lung tissue on the x-ray looks good on a CT scan. It looks great; there are no signs of parenchymal abnormalities on there, and that will guide us to say, well, maybe the muscles that actually do the breathing are the problem here. The gas exchange looks like it's intact, but there may be some anatomic abnormality leading to muscle weakness.

Sometimes we see signs on imaging that are associated with a chronic neuromuscular condition, and that may give us some hints. We can see sometimes significant scoliosis or an anatomic abnormality of the rib cage that suggests a childhood-onset neuromuscular disease. But in general, if the imaging is discordant with the degree of symptoms, those give us some clues.

Dr. Turck:
Now, in conditions like TK2d, respiratory compromise is often driven by muscle weakness rather than intrinsic lung pathology. So what clinical features help you recognize this pattern in practice?

Dr. Lussier:
Like I said, there's a lot of symptoms that pop up that are difficult to put into a box—whether it's airway disease, parenchymal lung disease, or if it's muscle lung disease—but you can tease out some that identify the muscle as the primary problem. Among those, we find that the obvious ones that people are most familiar with are orthopnea—difficulty lying flat, whether awake or asleep—and snoring. But the less common one that people pick up on is hypoventilation—so shallow breathing; the bed partner has to nudge you to see if you're actually going to breathe or not. Things that we find over time when your sleep is severely impacted are morning headaches, severe fatigue, and feeling like you never slept. And those are early findings that we say are muscle weakness. And those have to do with the natural trajectory of sleep-related hypoventilation that comes with a progressive neuromuscular condition.

Some of the things that we don't always pick up on are significant signs of neuromuscular disease as a cause for dyspnea. Along with

orthopnea, they are going to be immersion dyspnea, something like getting in a pool of water and somebody can't take in a deep breath anymore. They've coined this term 'bendopnea'—I can't bend over and tie my shoes because I'm too short of breath—and subtle things that family pick up on like hypophonia—I'm trying to activate some voice-activated system in my house, and it can't hear me; I have to try to yell, and I can't do it.

Other subtle things may be eating slower. It takes me longer to get through a meal because I have to take a deeper breath and hold my breath while I'm chewing, and then I have to take another breath before I swallow. And so naturally, my eating slows down. Sometimes it's a change in pitch. Sometimes I'm not able to sing, or sometimes it really is exertional dyspnea. Again, those are challenging to say, is this an airway problem, or is this a muscle problem? But when they're all taken together, that can be a sign that it's muscle weakness.

Dr. Turck:
Given the nature of some of these features, patients are often initially labeled with more common conditions, like COPD or asthma. In your experience, where do the misdiagnoses most often tend to occur, and how do you distinguish TK2d from primary lung disease?

Dr. Lussier:
We have a lot of guidance that tells us when we're looking at somebody's pulmonary function testing or imaging that says this is clearly going to be some sort of lung pathology or muscle pathology. But coming to that first is often challenging because COPD and asthma are clinical diagnoses, and a lot of these patients who come in may not have had child-onset disease—it may be in adulthood—they may have overlapping conditions, or they may have comorbid asthma or COPD. And so it's not necessarily a misdiagnosis so much as a delayed diagnosis or recognition that there is another problem.

The majority of patients don't come in reporting wheezing as their initial problem. It's usually dyspnea, and so the workup of dyspnea does and should continue to include a workup for things like asthma—something we're very comfortable treating and something that's familiar territory for most pulmonologists, and it's easy enough to rule out or to treat while we're looking for that other condition and that additional reason for dyspnea. And so it's not necessarily a misdiagnosis, but those things need to be ruled out in order to come to the appropriate diagnosis and also to treat the comorbid diseases. But what will make us stop and pause and say, no, this dyspnea is actually muscle weakness; it's going to be that restrictive pattern that we see on pulmonary function testing.

So when we do the test, we're looking at either a forced vital capacity or a slow vital capacity. We're going to look for how much air a patient can move in and out of their lungs in their single best effort. And if it's not enough, we say they're restricted, and that should lead us to say, well, is the restriction from parenchymal disease? Do they have a problem with diffusion capacity? Or is it a problem with weakness?

And then we'll go a step further and say, lay down flat and repeat this test. Does that provoke worsening of symptoms when you're lying down flat when your muscles are now at a disadvantage? So we do take a step when we don't get a response to the treatment for asthma or COPD. It's often how we come to the diagnosis of neuromuscular disease rather than a misdiagnosis. It actually guides us to that diagnosis in the end.

Dr. Turck:
For those just tuning in, you're listening to *NeuroFrontiers* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Bethany Lussier about recognizing respiratory manifestations of thymidine kinase 2 deficiency, or TK2d, in pulmonology practice.

Now, if we turn to the CHEST guidelines on respiratory muscle weakness, those emphasize the importance of evaluating neuromuscular causes in patients with unexplained restrictive physiology, particularly when there are reduced maximal inspiratory pressures or positional declines in forced vital capacity. With those recommendations in mind, Dr. Lussier, would you tell us how you apply them in clinical practice?

Dr. Lussier:
When we have a patient where we have a high suspicion for neuromuscular weakness as the reason for their dyspnea or we know what the diagnosis is—in this case, mitochondrial myopathy—that could be precipitating long-term hypoventilation, we know what we're looking for in the pulmonary function testing. Clinically, it's helpful to have a vital capacity or some measure of how well somebody's breathing in and out. And the guidelines suggest either using a slow vital capacity or a forced vital capacity, either one. The most important thing is how you use that number and some sort of measure of how strongly someone can suck in. So use either a MIP or a SNIP—a nasal inspiratory pressure—to measure how hard someone can suck in to say, are they having a risk for hypoventilation or nocturnal hypoventilation along with sleep?

And then they go further in those guidelines to get a strict measure of how forcefully someone can either cough or breathe out, and those allow us to intervene if somebody has a risk for poor airway clearance. And those are important clinically because I can address

that. If somebody has a muscle dysfunction that leads to weakness of either inspiratory or expiratory function, it's a mechanical problem, and we have mechanical fixes for that, whether it's cough assist devices or noninvasive ventilation.

Dr. Turck:
Now, another important but often overlooked aspect of TK2d is the role of gastrointestinal dysfunction. So how do features like dysphagia or impaired gastric motility influence your assessment of respiratory decline in these patients?

Dr. Lussier:
The gastric motility issues are significant, and bulbar weakness is also significant in TK2d. And both of them can be lumped into one major problem and some smaller ones. The major problem that we focus the most on is airway clearance. Bulbar issues along with esophageal motility issues can sometimes impact swallowing and the speed at which somebody can actually get a sufficient caloric intake, and we focus a lot on airway clearance in the pulmonary division.

The second portion that we need to focus on a little bit more is a problem that is poorly understood, but it's called aerophagia. Especially when I'm working with patients who are on noninvasive ventilation and if they have poor gastric motility and very restrictive physiology, they tend to have a path of least resistance—that's the stomach and not the lungs. So as I push air in with noninvasive ventilation, especially for extremely restricted patients where I'm using very high pressures, we end up with a problem with gut insufflation, and that can be extremely problematic. And so I'm always cognizant of poor gastric motility and gastric insufflation, especially at night in these patients. And it's a matter that is poorly understood. Gastroenterologists have a very hard time treating it along with us, and it's something that I think is an area of research in the future.

I'll also say gastric motility is another problem when it comes to malnutrition. Malnutrition exacerbates respiratory muscle weakness, and we know that. The other thing is that respiratory muscle weakness leads to very inefficient breathing. It's inefficient and ineffective, and we end up seeing that somebody will take two small breaths instead of one large breath, and it becomes very inefficient and they burn through far more calories. So for a patient who is starting to have trouble breathing, even if it's just at the end of the day and you notice that they're breathing at a rate of 25 instead of 15, that patient is burning through more calories than they would otherwise be. And so taking in enough caloric intake to support them nutritionally is a challenge because their needs are higher; their demand is higher. And at this point, it's harder to take it in, whether it's from bulbar weakness or just poor gut motility. And so the balance has shifted.

So it's really important that as a pulmonologist, a gastroenterologist, and a neurologist, we understand that the gastric motility has a big impact on someone's breathing.

Dr. Turck:
And finally, Dr. Lussier, once you suspect a patient has TK2d, what are some best practices for coordinating care among pulmonologists, neurologists, and gastroenterologists to support earlier diagnosis and better outcomes?

Dr. Lussier:
So when we see the constellation of neurologic symptoms—maybe some ophthalmoplegia, some gastric motility issues, or some bulbar weakness—getting that diagnosis changes everything. It's really challenging when the pulmonary function testing and the signs of hypoventilation suggest there is a mitochondrial problem here. It's at least a neuromuscular diagnosis, but we need that presumptive diagnosis. We need the muscle biopsy. We need the EMG nerve conduction testing in order to actually allow us to intervene. Static diseases are managed very differently from progressive neuromuscular conditions, and there's a natural trajectory that differs between the two.

And so having a good working relationship where if we know the symptoms are out of proportion, we can continue to dive deeper to get to the diagnosis and then intervene appropriately. That's really paramount to getting them the treatment that they need.

Dr. Turck:
Well, with those best practices in mind, I want to thank my guest, Dr. Bethany Lussier, for joining me to share her insights on respiratory involvement in thymidine kinase 2 deficiency and how we can better recognize it in pulmonology practice. Dr. Lussier, it was great having you on the program.

Dr. Lussier:
Thank you so much for having me. It was a pleasure.

Announcer:
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