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Cases in TK2d Care: Lessons Learned in Diagnosing and Managing a Rare Disease

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

Dr. Turck:
Welcome to *NeuroFrontier*s on ReachMD. I'm Dr. Charles Turck, and joining me to offer his insights on patients with thymidine kinase 2 deficiency through clinical cases is Dr. Bruce Cohen. Dr. Cohen is a pediatric neurologist and the Chair of the NeuroDevelopmental Science Center at Akron Children's Hospital in Ohio. He's also a leading expert in mitochondrial diseases. Dr. Cohen, thanks for being here today.

Dr. Cohen:
It's great being here, and I appreciate the opportunity to speak to you and our audience.

Dr. Turck:
Well, to get us started Dr. Cohen, how do you identify patients with suspected thymidine kinase 2 deficiency, or TK2d for short? What does their clinical presentation look like?

Dr. Cohen:
So the clinical presentation is quite variable and really depends on the age. I think the core clinical feature is myopathy in these patients, but the nuances of exactly how these patients present vary from patient to patient and in the different age ranges. Typically, we think about patients being under a year of age, between one year and 12 years of age, and greater than 12 years of age in terms of exactly how they present.

Dr. Turck:
And then once you identify patients with possible TK2d, Dr. Cohen, what steps do you take to diagnose them?

Dr. Cohen:
The way I think about these patients is when I initially see them, I wouldn't necessarily jump to TK2 deficiency right away. I would see a patient with a neuromuscular presentation, and then start the differential diagnosis based on the examination. Again, if we look at infants with TK2d, those patients present generally with a myopathic or myopathic encephalopathic form of the disease where they're very hypotonic, have respiratory difficulties, have feeding difficulties, and often present with lactic acidosis and elevated CK enzyme. Adults typically present with a milder form and generally slower progressive form of the disorder, generally with myopathy and often with progressive external ophthalmoplegia. The older children present with sort of a disorder that can go halfway in between the two age ranges.

And of course, the differential diagnosis on these patients is enormous. When I started training, it could take months or years to reach a diagnosis – often not a confirmed diagnosis because we didn't have genetic confirmation back then. Now with genetic testing, we can reach a diagnosis rather quickly. And I'm happy to go into some of the details.

Dr. Turck:
Oh, yeah, if you would. What else does our audience need to know about genetic testing?

Dr. Cohen:
I think that's best addressed with an example of a patient I cared for that had an infantile onset of the disease. I met the child when she

was 8 months old. She had gastric esophageal reflux since birth and had a few vomiting spells. By report, she had a head lag from the first day of life. Never really was able to support her head in any fashion and certainly not when placed within a sitting position, and never actually reached the point that she could sit. By 6 months of life, was felt to have decreased limb movements. Her examination showed that she was bright-eyed, engaged socially, but had decreased limb movements. Biochemical features of her condition showed an increased anion gap on basic electrolyte testing, and she was found to have a mild lactic acidosis, in the 3-millimolar range. Her CK was slightly elevated for age and her size, at about 300, and I think the telltale sign that we were thinking about TK2 was an elevated GDF-15. GDF-15 – growth differentiating factor 15 – is a biomarker in evolution that seems to be elevated in mitochondrial myopathies. Now even then, we didn't have a firm diagnosis of any disorder, though we were thinking down the mitochondrial pathway just because of her presentation of severe hypotonia. We did do SMA gene testing, and that was normal. We looked at POLG, that was normal. We were also looking for a mitochondrial DNA mutation that is seen in the benign cytochrome c oxidase reversible form of myopathy, and that was normal. And then we went to whole exome testing, and that confirmed the TK2d diagnosis.

Dr. Turck:
Would you tell us about the health burden and unmet needs patients with TK2d have?

Dr. Cohen:
The health needs have to do with the myopathy and the other phenotypic components of this disorder, which can extend beyond the muscles and also can involve the brain, the heart, the kidneys, and the nerves.

I think a good example of what some of the unmet health needs are can be demonstrated by an adult patient I saw years and years ago and really didn't know about his TK2d diagnosis until many years after I saw him. I met a colleague who referred him to me initially from another part of the country who said they got a whole exome, and it was TK2d. But he presented with mild onset weakness along with a progressive external ophthalmoplegia that he had actually had for years and never really addressed that PEO problem. He also had type 2 diabetes and, probably in retrospect, had metabolic syndrome as well as a comorbid factor. His other medical problem was obstructive sleep apnea, and he was on a C-PAP machine. On examination, he had progressive external ophthalmoplegia. He had a mild myopathy. He had a mild neuropathy that may or may not have been related ultimately to TK2. It could have been certainly from the diabetes as well. His weakness was more along his oral pharynx and axial system with some neck weakness, some swallowing weakness, some dysphonia as well. His examination led me to obviously think about this being a neuromuscular disorder and maybe a mitochondrial disease. The CK was chronically elevated, in the 800-1000 range. He really didn't have any lactic acidosis. Because of the PEO, I went down the mitochondrial route. He did not want a muscle biopsy, so we did mitochondrial DNA deletion studies on blood, which is not that sensitive of a test and that was normal. I was concerned about oral pharyngeal muscular dystrophy because he fit that pattern. That gene testing was normal. I was thinking about POLG disease and Twinkle mutations. Back then, we could do single gene testing. There was no panel testing available, and both of those were normal. His neurologic features progressed slowly over time, and it wasn't until years later, when whole exome testing was available that his home clinician made that diagnosis based on exome testing. His unmet needs had to do with mainly his myopathy, some degree his neuropathy, and his ventilatory issues and swallowing issues.

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. Bruce Cohen about a myopathic form of mitochondrial disease, called thymidine kinase 2 deficiency, or TK2d.

Concerning those unmet needs we just discussed, Dr. Cohen, how do they contribute to your challenges in the clinical management of TK2d?

Dr. Cohen:
So once we have the diagnosis of TK2d, I think it ends up being rather easy to figure out how to manage the symptoms of the patients. Now we're not talking about curing the patient; we're talking about managing the symptoms. And I think as most neurologists and clinicians, we make good use of our rehabilitation services and our therapy services, such as physical therapy, occupational therapy, and speech therapy. So I think that's really a bedrock of how we manage patients. As with the patient I discussed, respiratory difficulties and diaphragmatic weakness is common, and in his case, his sleep apnea could have been due to the effects of him being overweight but more likely due to the fact that he had diaphragmatic weakness from the TK2d. And obviously, ventilatory support both at night and sometimes during the day with noninvasive therapies can be helpful. And finally, some patients do have difficulty swallowing and may need assistance with invasive procedures such as G2 placement. The younger you are at diagnosis, the more likely you're going to need all of these therapies.

There are occasional patients with cardiac involvement, renal involvement, and liver involvement, and these organs need to be screened for dysfunction at least initially at the onset of the disease, and then as necessary as time marches on with the patient.

Dr. Turck:

Would you recommend some strategies for patient-centered care in the management of TK2d?

Dr. Cohen:
So I work at a children's hospital with a very robust palliative care program, and so any patient with TK2d would be referred to this program. This is not a hospice program. We're talking about palliative care, and they really take over medical home management of these patients. So they're looking at social factors as well as medical comorbidities that would occur along with the illness. You know, obviously, patients with TK2d are more prone to respiratory infections and the consequences of those respiratory infections because of the risk of hypoventilation. So we really want our patients to have a solid medical home. Sometimes that medical home exists within the neurology practice. Sometimes it exists within the primary care practice. Sometimes there's a service available at the hospital. Again, this all depends on what the local factors are.

Dr. Turck:
Now as we end our program, Dr. Cohen, are there any additional thoughts about TK2d you would like to share with our audience today?

Dr. Cohen:
I believe there's hope on the horizon for TK2d, at least for some of the patients with this disorder. We know that the abnormal enzyme function results in abnormal concentrations of nucleotides within the mitochondrial DNA building block pool, so when you have TK2d, you get either decreased formation of mitochondrial DNA or mitochondrial DNA that has point mutations and breaks within it that results in inability for that mitochondrial DNA to ultimately form proteins that are necessary for mitochondrial function. By reestablishing normal thymidine levels within the mitochondria, one can see a benefit in terms of neuromuscular stability or actually improvement in strength in clinical studies. I think these are on the short-term horizon. On the long-term horizon, may actually be actual gene therapy.

Dr. Turck:
Well, with those final thoughts in mind, I want to thank my guest, Dr. Bruce Cohen, for joining me to share his experience in the management of patients with thymidine kinase 2 deficiency. Dr. Cohen, it was great having you on the program.

Dr. Cohen:
Thank you very much. I appreciate the opportunity to let the audience know about this rare but fascinating and hopefully treatable illness.

Announcer:
This episode of *NeuroFrontiers* was supported by UCB. To access this and other episodes in this series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!