Video Transcript

Editor's Note: *This is the transcript of a live webcast presented on October 12, 2023. It has been lightly edited for clarity.* A video recording of the webcast is the core resource of this educational course. To obtain credit for participation, go to https://www.annenberg.net/courses/landingPage.php?courseID=60530

Review of Mitochondrial Function – Background & Introduction

Mary Kay Koenig, MD: Mitochondria are considered the energy center of the cell. They're found in the cytoplasm as dynamic networks that adopt energy production based on cell needs. Additional functions of the mitochondria include: storing calcium for cell signaling activities, generating heat, and mediating cell growth and death through apoptosis. The structure of the mitochondria is unique in that they have their own piece of DNA. This is the only intracellular extranuclear piece of DNA, and it is found in almost all the cells in the human body. Mitochondria also contain their own transcription and translational network, including ribosomes that help maintain their mitochondrial DNA. The energy-generating process of the mitochondria occurs through oxidative phosphorylation, which is a process that occurs along the membrane spaces of the mitochondria. This process produces approximately 90% of the body's energy in the form of adenosine triphosphate, or ATP.

Mitochondrial diseases form a group of heterogeneous diseases caused by genetic mitochondrial dysfunction. Both mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) are responsible for the structure and function of the mitochondria and ATP generation. Primary mitochondrial disorders are caused by mutations in either the maternally inherited mtDNA or one of the many unclearly inherited mitochondrial genes. Mitochondrial defects can affect any tissue or organ and they severely impact daily living and quality of life in patients who carry them. They typically present as neuromuscular or metabolic conditions, and tissues with high energy requirements are particularly vulnerable, especially the brain, the sensory epithelia, and extraocular, cardiac, and skeletal musculature.

This diagram represents some of the organs that are commonly affected and associated in patients with mitochondrial disease. Starting with the nervous system, patients often have tremors, seizures, developmental delays, hearing loss, loss of cognitive functions. They frequently will have strokes, often in early age, difficulty with balance, and issues like ataxia, or problems with peripheral nerves leading to sensory loss or even motor function.

Relative to the heart, cardiomyopathy and conduction blocks are very common. Liver failure is something we see frequently in patients with mitochondrial DNA depletion syndromes. We also see findings of fatty liver or hepatic steatosis. In the kidneys, patients may present with Fanconi syndrome, nephrotic syndrome. One of the most classic features of mitochondrial DNA diseases is ptosis, or drooping of the eyelids, and ophthalmoplegia, or difficulty moving the eyeballs. As a result, patients end up looking forward with an inability to move their eyeballs in any direction. Additionally, loss of vision from things like retinitis pigmentosa or optic atrophy and cataracts are also seen.

In the digestive tract, you may see acid reflux, vomiting, chronic diarrhea, or even constipation or intestinal obstruction. Diabetes is a very common feature seen in patients with mitochondrial disease, and it's often very different from the type of diabetes seen in other patients. Typically, the onset is in adulthood and yet it is often insulin-dependent and more difficult to control than your typical forms of diabetes. In the muscles, we'll see muscle weakness, exercise intolerance, cramping, and often we'll have elevations in creatine kinase (CK) levels that can sometimes lead to myoglobinuria. In the reproductive system, we can see infertility in either males or females, and women will frequently have recurrent pregnancy loss.

TK2, or thymidine kinase 2, is a nuclear-encoded enzyme that is important for mtDNA maintenance and function. TK2 is an enzyme that is required for the mitochondria to make proper mtDNA. And if the mitochondria are not able to properly make their mtDNA, then none of the normal mitochondrial functions will occur. As shown in this diagram, you can see TK2 labeled and TK2 functions to recycle thymidine, which is one of the building blocks needed to form the dinucleoside phosphates necessary for mtDNA maintenance and replication. Therefore, a patient with a TK2 deficiency is not able to properly

recycle their thymidine to allow for that dNDP pool to be maintained and allow for proper maintenance of the mtDNA.

TK2 deficiency is a rare, inherited mitochondrial disease that's caused by biallelic mutations in the TK2 gene. It is a nuclear gene, inherited in an autosomal recessive manner, so 1 copy from each parent. Deficiency of the TK2 enzyme causes a problem in the replication of the mtDNA. and patients will develop 1 of 2 problems. The first is, they will not be able to copy their mtDNA appropriately, so over time, as the mitochondria replicate themselves, they copy the shell but they're not able to properly copy the DNA. The result of this will be a depletion of mtDNA. A cell will be full of mitochondria that have no DNA in them, and we call this a mitochondrial DNA depletion syndrome.

Another problem is in the proofreading or the maintenance structure of the mtDNA, referred to as a multiple DNA deletion problem. Patients could copy their mtDNA incorrectly and, over time, they develop multiple breaks in their mtDNA leading to multiple deletions. Although they have a normal amount of mtDNA, that mtDNA is nonfunctional because it has multiple breakpoints in it that it shouldn't have. Muscle tissue is most susceptible to TK2 deficiency and patients present with a variety of symptoms, but most prominently they will have progressive muscle weakness leading to eventual respiratory failure.

This is a diagrammatic representation of the TK2-deficient mitochondria. On the left-hand side, you see a normal mitochondria. The little yellow ovals represent the TK2 enzyme and the little hexagons represent the nucleosides. In a patient with normal mitochondria and normal TK2 function, what you see is a normal amount of TK2 enzyme, you see a normal amount of the DNA building blocks, the nucleosides, and you see a normal amount of mtDNA being formed. In this case, the mitochondria is able to function normally and is able to do all of the processes it needs to do, including produce ATP.

On the right side, you see a patient with TK2 deficiency and what you notice is that within their mitochondria they have a smaller amount of TK2 enzyme, and in that cell they have a smaller amount of nucleosides (the little hexagons). Thus, because they have less nucleoside, they're able to make less functional mtDNA, and this produces less ATP, which allows for the progressive muscle weakness characteristic of this condition.

We know that about 1 in 4,300 individuals in the United States has a mitochondrial disease. TK2 deficiency was first described in 2001 in 4 children who had severe muscle disease. As of 2022, there have been less than 120 individuals described in the medical literature with TK2 deficiency, but we are starting to recognize more and more patients with this condition the more we know about it and the more we're looking for it.

Clinical Presentation

We now know that in addition to the early-onset phenotype, where children present less than 1 year of age, there's also a childhood- onset phenotype, where children can present between the ages of 1 and 12. There's also a later-onset phenotype that tends to present in people who are older than 12, and these patients may actually not present until adulthood.

Early-onset patients present with what we call the severe myopathic form. This patient has severe progressive myopathy, severe intestinal dysmotility with failure to thrive, and early respiratory failure. They also have a variety of other symptoms that you will see, including cardiomyopathy. They may have seizures and encephalopathy, developmental delay, microcephaly and optic atrophy.

The childhood-onset patient, the patient who presents after the age of 1 but before the age of 12, also has progressive muscle weakness. They have more obvious eye findings, like chronic progressive external ophthalmoplegia (CPEO). They also have more noticeable ptosis and will also develop respiratory failure. You'll see more of the dysphagia and dysarthria. They develop more hearing loss, more of the cognitive decline. They also have cardiac involvement with arrhythmias and prolonged QT syndrome. They may develop renal tubulopathy as well as some endocrine issues, leading to gynecomastia and bone fractures.

The late-onset patient, the patient presenting after the age of 12, also develops progressive myopathy. They also develop the CPEO, ophthalmoplegia with ptosis, eventually leading to respiratory failure. They have very prominent bulbar involvement, dysphagia, dysarthria, hearing loss, and you see a prominent sensory peripheral neuropathy in these patients.

Now, let's go through cases for each example of the age of onset for TK2. First, Quinn is an infant with early-onset TK2 deficiency. Again, less than the age of 1 when she started having symptoms. She was an infant born at term following

an uneventful pregnancy. At birth, she appeared quite healthy and had a normal exam. She met her early developmental milestones, in fact, rolling by 4 months and sitting on her own by 6 months. By 8 months, her parents noticed that she had lost some of these skills and started becoming extremely weak. By 12 months, she was severely hypotonic. She was no longer able to move volitionally and she developed respiratory weakness. Her cognitive function seemed to be appropriate. She continued to laugh and smile at people who came into the room and entertained her. She ended up needing a G-tube by 12 months for nutritional support. She required a tracheostomy by 18 months because she could no longer maintain her own respiratory status and, unfortunately, she passed away a little past her second birthday from pneumonia after the tracheostomy had placed. This is a very classic case of early-onset TK2 deficiency. It's very severe, very rapidly progressive, and leads to very early respiratory failure.

Our next case is Cora. This is a child with childhood-onset TK2 deficiency, again usually presents between 1 and 12 years of age. Cora first presented when she was 17. She had an uneventful early childhood development. She had no concerns at birth. She actually started walking at 12 months of age. What her parents described is that when she was a little kid in preschool, they would notice the other kids pop up off the floor. So, you'd be sitting in circle time, and everybody would just jump up off the floor, but Cora didn't do that. Cora would have to use her hands to help her get up off the floor. And she tried to play sports and, in fact, she was active in dance, but she really wasn't that good at it and she couldn't keep up with the other kids her age.

At 14 years of age, Cora started having problems with fatigue, and then began complaining to her parents that she felt weak and was having cramping in her muscles. She started noticing that she couldn't climb stairs very well and she was no longer able to brush her hair. By the age of 16, she was wheelchair-bound. Although it seemed Cora was, early, meeting all of her milestones, by preschool she was having some symptoms of myopathy.

An EMG was performed that showed myopathy and then a muscle biopsy was performed that showed signs of mitochondrial myopathy. It actually showed ragged red fibers. Mitochondrial DNA quantification was performed. This is a study assessing how much mtDNA is present in the muscle tissue compared to the nuclear muscle tissue. And there's a normal amount that should be present. In Cora, it was 11% of control, and this is definitive for mitochondrial DNA depletion. Genetic testing was performed and identified biallelic compound heterozygous pathogenic variants in her TK2 gene.

Since her diagnosis, Cora has experienced rapidly progressive weakness. She's developed bulbar symptoms leading to weight loss, choking and worsening pulmonary function. When she was 15, she had pulmonary function testing done that showed a forced vital capacity (FVC) that was 37% of predicted and a forced expiratory volume at 1 second (FEV1) that was 41% of predicted. She does use a bilevel positive airway pressure (BiPAP) machine most of the time and is followed regularly by a pulmonologist. She has shortness of breath and difficulty breathing, even when she tries to talk, and she is well on her way to requiring invasive ventilation to maintain her respiratory status at the age of 17.

On physical exam, Cora was alert, engaging, and very intelligent. She spoke in short sentences, but her speech was limited by shortness of breath. Her content was appropriate; there didn't seem to be any sort of encephalopathy or loss of cognitive function. Cranial nerve exam showed bilateral ptosis, and she actually had to tilt her head back so she could see. Her extraocular muscles were mostly intact, but there was some limitation of upgaze. She had a very mild myopathic appearance. Facial muscles were weak, and there was severe proximal muscle weakness. She was unable to raise her shoulders or hips anti-gravity (2/5). She was able to move both arms, but not really against gravity, and her hands also had moderate grip weakness. This was again at the age of 17.

She was unable to get up from her wheelchair without assistance. She was able to stand, but her feet were everted and she was very lordotic. She had decreased reflexes in her upper extremities and completely absent in her lower extremities.

Again, this is a very classic case of a more childhood-onset or the mid-onset range of TK2 deficiency, presenting a little bit later, progressing a little bit slower, but still progressing pretty rapidly to respiratory failure within 10 years of onset of symptoms.

Isla is a case of late-onset TK2 deficiency. This is a 26-year-old young lady with a normal early childhood and development. She had absolutely no sign of motor involvement until the age of 13 years. At 13, she started complaining of muscle pain, and since that time, she's had a progressive decline in her muscle function with pain.

Isla had a muscle biopsy performed when she was 15, 2 years after onset of symptoms. Her biopsy also showed ragged red fibers. Her mitochondrial DNA content was 42% of control. What I want you to notice is that her mitochondrial DNA content was actually better than it was in the last patient. She had more preserved mitochondrial DNA replicating ability, which is probably why she had later onset of disease. She had genetic testing done that showed compound heterozygous pathogenic variants in her TK2 gene and her muscle biopsy showed multiple mitochondrial DNA deletions, not surprisingly. This young lady was wheelchair-bound by age 21, 8 years after the onset of her symptoms. At 26 years of age, she was cachectic; she had a poor appetite and reported that she choked a lot when she tried to eat. She had shortness of breath at rest, pain and weakness with any attempt to move, and she complained of tinnitus. She did not note hearing loss at this point, but she did have tinnitus.

On exam, Isla weighed 37 kilos (about 80 lb) and her height was 164 cm (about 5'8"). She was very interactive, and her speech content was appropriate. She was a little bit dysarthritic. Her speech was very limited by shortness of breath; she could only say 2 or 3 words at a time before she'd have to stop and gasp for air. She also did not have any signs of dementia or encephalopathy. Her cranial nerves were intact. There was no ptosis and there were no signs of extraocular movement involvement. Sensation was intact. She had almost no muscle bulk and she had severely decreased tone and strength. Her proximal strength was 3/5 in the upper extremities; 2/5 in the lower extremities, so she couldn't even do anti-gravity in her lower extremities, and her distal strength was about 3/5 in the upper and lower. She could move a little bit anti-gravity, but not much. She was also able to get up from a chair, but she required significant assistance. She was able to stand and walk a few steps, but her gait was wide and waddling and she was very lordotic.

One thing I hear about a lot while working in a mitochondrial clinic is this concept of the diagnostic odyssey, or how long it takes to receive a diagnosis. All 3 of the patients I just presented were diagnosed relatively quickly with their mitochondrial disease. It took several years for them to achieve a diagnosis and I can't even imagine, as a parent, where your child is becoming progressively weaker to a point where they're in a wheelchair and you're still waiting for the why. Someone's still waiting to tell you why is it taking [so long], why is this happening to my child. So, even when we say these patients were diagnosed relatively quickly, 3 years is a very long time to wait for a diagnosis when your child has gone from walking, running and jumping to wheelchair-bound.

This diagnosis can be quite complex and it's quite burdensome, because the clinical picture often isn't very clear and patients often require multiple consultations and go through multiple tests. Myopathy, which is what these patients presented with—progressive muscle weakness—it's a symptom, not a diagnosis. When patients are first presenting, they very rapidly will come to this diagnosis of myopathy or this recognition of myopathy, but that's not really telling someone why—why you're like this, why your child is no longer walking. Leading to that final step is really important in getting to that why. One of the things that's become more and more available over the last few years, and more and more important to do early in the diagnostic process, is this broad-spectrum genetic testing. It's now really indicated early in the diagnostic process to decrease this diagnostic odyssey.

When you have a condition like myopathy, it's no longer really recommended that you try to do targeted testing. What we used to do and early in my career, this was what we did, we had limited availability of genetic testing. You used to have to try to guess what you thought it was and then you could send that gene. And so we would do a big work-up, we would often do electromyographies (EMGs) and then we would do muscle biopsies, we would do all kinds of stains on the muscle biopsies and you would try to figure out exactly what the patient had. I think they have x, y and then you would send a genetic test. Well, it's not that. Okay, let's go back to the drawing board. Let's look at the patient again. Let's see if we can figure out what they have and then, if we can't figure it out, then we'll do some additional testing and then we will send the next genetic test.

Often, it was this long process of sending individual genetic tests or even maybe small panels and trying to obtain an answer. With the advent of these broad-spectrum genetic tests like whole-exome sequencing or whole-genome sequencing, and our ability to get these covered more and more and more by insurance panels, we no longer have to do this. Now, as soon as we recognize someone has myopathy, we don't have to spend our time doing a bunch of invasive, timely tests that may or may not point us in a direction and may or may not lead us to guessing correctly. What we're able to do now is do very broad-spectrum testing and do it very early in the diagnostic process to help point us to a correct diagnosis a lot earlier.

There was a survey conducted of individuals who were eventually diagnosed with mitochondrial disease. It looked at 210 patients. These were people who were enrolled in a Patient Contact Registry through the Rare Disease Clinical Research Network, the RDCRN, sponsored by the NIH. Participants saw an average of 8 clinicians prior to their diagnosis, 54.6% of them received more than 1 non-mitochondrial disease diagnosis prior to being diagnosed with their mitochondrial disease. In pursuit of their diagnosis, almost 85% had blood tests, 71% had muscle biopsies, 60% had MRI scans, and 38.6% had urine organic acids. 39.5% of them underwent mitochondrial DNA sequencing (19% had nuclear gene panels and 11% had whole-exome sequencing). In today's day and age, that whole-exome sequencing should be a lot higher percentage and it should be a lot earlier in the diagnostic process.

Approach to Diagnosis

What are our barriers to early diagnosis? First, a lack of training among clinicians in mitochondrial disease recognition and diagnostic evaluation. I say all the time to our trainees who come out of our residency program and tell me all about the mitochondria and mitochondrial disease, when I was in medical school, no one talked about mitochondria or mitochondrial disease. The majority of physicians out there in practice today never heard about mitochondria or mitochondrial disease when they were training. Although the young guys know about it, most physicians who are in practice were never trained on mitochondrial disease. We are working very hard to start educating—through programs like this—physicians in practice, about mitochondrial disease, but it is a time process. It takes time to disseminate that information and it is getting better.

With one of the barriers being that the majority of physicians in practice have never been trained on mitochondrial disease recognition and diagnosis, I applaud you for being here today and learning about it.

Another barrier is a failure to obtain genetic testing or limiting testing to specific genes. Again, the genetic testing is advancing so rapidly and unless we're staying up to date on what these latest genetic tests are, we're often lagging [behind by] a few years on what's available, as well as what the insurance companies will pay for. Although doing specific targeted analysis was initially the preferred method of genetic testing, that has now been shown to not be cost-effective anymore. By the time we guess and miss and guess and miss and guess and miss, 3 or 4 times, we're better off just sending broad-spectrum whole-exome sequencing from the start. And insurance companies have started coming to that realization, and the reimbursement for this type of testing is becoming easier and easier every day. Therefore, it's actually no longer recommended that we do targeted analysis. It's now recommended that if you have a patient with a very broad diagnosis or a very broad presentation like myopathy, that you do broad-spectrum genetic testing early in the diagnostic process.

Still another barrier is a disparity in medical care based on geography and exposure to expertise, and we all know this. If you live down the street from a major academic center, you may have exposure and availability of more advanced testing just by geography and that is no fault of the patient and no fault of the physicians. It's just the way things exist in our country.

How do you diagnose mitochondrial disease? Well, the diagnostic approach involves a specialist clinical assessment, biochemical analysis and molecular genetic testing. Broad-spectrum genetic testing is indicated very early in the diagnostic process. Whole-exome sequencing or whole-genome sequencing are the highest yields and the most cost-effective. Why do we care about getting this genetic process or getting this genetic diagnosis? It tells us all sorts of things about the patient, what they have, what to expect, what's their prognosis, what's the risk for family members. One of the things that's been advancing rapidly in mitochondrial medicine is clinical trials, and, in a patient who has such a severe neurodegenerative disease like TK2 deficiency, if there's a clinical trial out there that they can enroll in, we need to be able to know and offer them that information. And if we don't know what their genetic diagnosis is, 1, we don't know what trials are available to them and, 2, they're never going to get in a trial without that molecular confirmation. Thus, genetic testing is crucial to help them understand their prognosis, know what their genetic risks are for passing these conditions on and what the risks are to their family members, and helping them find potentially available therapies that are either approved or are in clinical trials at the current time.

Right now, if you look at all the mitochondrial disease specialists and you look at all the patients that they have, that they know have a mitochondrial disease, we say we can identify the molecular reason for their mitochondrial disease in somewhere between 50% and 70%. So, where's the other 30% to 50%? And why do we not know what their genes are? Well, this number is much higher than it was 10 years ago, and the reason is that we just don't know all those

genes yet. We know that there are probably close to 1,500 nuclear genes associated with mitochondrial function and required for the mitochondrion to function properly. And so we don't know diseases associated with all those genes yet. We're still working on it. What I tell my patients is this is really a fault of science and we're still working on it; 15 years ago, we could only diagnose 20% and now we can diagnose almost 70%. In another 15 years, we're going to figure you all out, so just hang in there and we keep looking.

Another caveat here is that if you have a patient who you've been following for many years with a myopathy or with a mitochondrial disease, it's time to retest them. If they haven't been tested in a few years, the testing is better. We know a lot more than we knew a few years ago, so always revisit that potential diagnosis and see if new testing is indicated.

You need to have high index of suspicion to diagnose a mitochondrial disease. You should do a detailed assessment and exam, a pedigree analysis always helps when you're looking for a genetic condition. Phenotyping of symptoms, biochemical analyte testing in the blood and the urine. We try to stay away from invasive testing, like cerebrospinal fluid (CSF) analysis, initially. You can do some screening labs, again blood and urine testing, to look for other organ involvement, and then step 2 is now genetic diagnostic testing. It really used to be muscle biopsy and it's just not anymore.

We now move to either whole-exome or whole-genome sequencing and this can be done in blood, typically blood or buccal cells. Occasionally, you can do it in urine, but really blood or buccal cells are the best specimens to do this type of testing in. And often you want to do it both in the patient and in their biological parents. This is going to give you the most information and, as I said, insurance companies are rapidly coming on board with paying for this testing. In most patients, you are going to get a diagnosis and that allows you to proceed with treatment and management. So, either standardized clinical care or you can try to help the patient find a clinical trial.

If your genetic testing is negative or inconclusive, at that point we do sometimes move on to muscle biopsies or skin biopsies, sometimes the liver, depending on the symptomatology of the patient. You can look at histology, immunochemistry. You can actually look at the mtDNA content, or sequencing in the muscle or the liver. You can look at CoQ10 levels, and frequently we send these samples for research testing and that's how we're able to identify new genes all the time.

As far as TK2 goes, I always say the signs and symptoms of TK2 deficiency are not particularly subtle, particularly not in a young patient. This is not a kid that the pediatrician sees and says, "Hmm, I wonder what's going on with this kid." These infants, especially the early-onset infants, are weak and they are losing milestones pretty quickly. The myopathy is pretty readily recognized and these patients very frequently get referred to a neurologist quickly. I think the biggest barrier here is getting them in to a neurologist. There is still a shortage of child neurologists in this country and it's still very hard to get this kind of patient into a neurologist. As a general pediatrician, there's really 2 options that you would have. One is, call the neurologist. If I ever get a call from a pediatrician that says I have a kid that could sit up a month ago and can no longer sit up, that kid gets in my clinic this week because he's more important than all the headaches and first-time seizures and everyone else I've seen.

Another option is sending them to an ER where you know there is a pediatric neurologist. Although you may not consider this an emergency, it is something that does need to be seen on an urgent basis and, at a minimum, you can get that child connected with a neurologist in that manner. But I would always just try calling your local child neurologist and letting them know you have a case that you think really needs to get seen quickly and, almost always, they're going to work that patient in.

The mid-onset, early-childhood patient, these kids are typically going to present with this tripping and falling. This is a kid who started walking, they were walking fine and then, all of a sudden, the parents call and say their kid is falling down all the time and I don't know why, they're tripping all of the time. This is a really classic sign of muscular dystrophy or myopathy onset, and these patients very frequently get referred out very early and they generally get to neurology pretty quickly. But again, if your appointment is too far back, call your neurologist and let them know that this is someone you think needs to get seen sooner.

Where we run into trouble is if these patients get referred to a non-neurologist. So, every now and then, we see a child who's tripping get referred to an orthopedist because they think it's something like flat foot or a foot drop that needs a brace, or they get referred to a therapist and that can delay the referral

to a neurologist. So, just keep in mind, these kinds of presentations of tripping, falling, hypertonia, weakness, especially if it's a loss of function, that really requires a neurologic referral, even if you can get into the orthopedist faster, because what you don't want to do is delay the neurology referral.

The group that's often getting missed with TK2 deficiency and getting a real long delay in their diagnosis are these older patients, the patients who are presenting after the age of 12. The onset of symptoms in these patients is much more insidious, and teenagers are difficult, anyway, because they'll start telling their parents, "Oh, my muscles hurt, oh, I'm tired, oh, I don't feel good, oh, I feel weak." And teenagers just complain a lot and so, a lot of times, parents just chalk it up to them being a teenager. And these patients frequently will have weakness for years before they get referred to a neurologist at all. I think that it's this group of patients that requires the most attention and the most care.

A good neuro exam really can pick them up. They are weak on exam and just doing a good proximal muscle exam really will bring that out in these patients much sooner and will help you identify these patients a lot sooner. And then again, any time you see these patients, they should get referred to a neurologist and, because of the nature of these kinds of conditions, any time you diagnose something like a TK2 deficiency, this is an ultra-rare mitochondrial disease, this patient really ought to be seen by a mitochondrial specialist. This is a patient who you really do want to get into some kind of a treatment, a center or treatment plan and, as a general neurologist or a general pediatrician, you probably don't have the time for looking up this disorder, learning everything there is to learn about it and figuring out exactly what the best treatment approach is. Thankfully, there's now been a Mitochondrial Care Network set up across the country that was developed between the Mitochondrial Medicine Society and some of the patient advocacy groups to have these centers located, to try and have a place for you to refer these patients to who have these types of mitochondrial diseases where they can get that specialized care. I'm located down here in Houston, Texas and what we do is we try to work with the local physicians and, as you can see, we, and Colorado, are kind of silos in the middle of the country and so we get a ton of referrals from patients who are far away. And it's not realistic to expect this patient to come and see me every month or every 2 or 3 months, so what the mitochondrial centers will often do is say, I'll see you once a year and then I will consult back with your local physician to help them manage you. If your patient is able to travel to one of the mitochondrial centers, then it is often worthwhile to get that consult and get that opinion and have them seen.

There's actually a listing here on this next slide. There is a big gap in the middle of the country of mitochondrial centers. We are aware of that and trying to address it. Unfortunately, there's a big gap of medical care in general in that region as well. Some of these centers also do teleconsults. So, if you have a patient, I would suggest just Googling the Mitochondrial Care Network and going to their website and seeing if perhaps you can find someone that can do a telecare consult if the patient can't get to one of the care centers. But again, it's worth getting an opinion and getting a consult on record so that you can get some guidance on what the most up-to-date therapy is.

Now, let's talk about the standard of care for TK2 deficiency. Current treatment—what do I do when I see these patients? Respiratory. I can't tell you, every patient I've ever seen with TK2 deficiency has come into me without a pulmonary evaluation. These patients are so profoundly weak and often, when you're talking to them, they cannot get full sentences out because of the weakness. They need a ton of respiratory support and they will require mechanical ventilation eventually. Therefore, early respiratory therapy leads to preservation of lung function. The more respiratory clearance they get, the more BiPAP they use, the stronger their lungs are, the longer we can preserve lung function. As soon as the patient is diagnosed, they need to start seeing a pulmonologist immediately.

Feeding tubes. Nutrition is hugely tied to strength. We all know that people who are malnourished are weak. You can't get enough protein in, you can't make your muscles, you can't stay strong. So, nutrition is very important. Ensuring that your patient is getting enough food, enough nutrition. Patients often have difficulty swallowing, the food gets stuck, they choke. They often have a decreased appetite. So, sometimes they need tubes in order to help maintain their nutrition.

Wheelchairs and physical therapy. Making sure they're following up with either rehab or a physical therapist who can ensure they have the appropriate equipment to keep them from falling and hurting themselves. And then most mitochondrial physicians will have what we call a cocktail, which is a series of vitamins.

What are the unmet needs? We need to stop the muscle weakness and chronic fatigue, improve the GI problems. It'd be great if we had a way to reverse the muscle weakness, gain function, halt disease progression and prolong life.

Emerging Treatments

There is now an investigational therapy for TK2 deficiency. It is an oral investigational drug called MT1621 and it's also referred to as a nucleoside therapy or deoxynucleoside substrate enhancement therapy (SET), which is a mixture of deoxycytidine and deoxythymidine. And again, it's given orally. So, the 2 pictures on the left here you've already seen. The picture on the right is a patient who's been treated with MT1621. This is an oral medication that replaces the missing nucleosides. If you recall, in TK2 deficiency, the underlying problem is that the TK2 enzyme is unable to recycle the nucleosides and so you have a nucleoside deficiency within the mitochondria and you're unable to maintain your mtDNA.

The way that this therapy works is by replacing the missing nucleosides. So, the medications are given orally, and they effectively replace the missing nucleosides to allow the mtDNA to be maintained appropriately. It is as simple as that. It doesn't address the genetic defect, it does nothing to the TK2 enzyme, it just replaces the missing substrate.

There are 3 studies that have been done. One of them is a retrospective study, 1 is an ongoing prospective, open-label study looking at these patients, and then there's a retrospective chart review that's also been done, looking at the natural history of this condition.

The phase 2 retrospective medical chart review looked at 38 patients, pediatric and adult, with TK2 deficiency treated with MT1621 for an average of 72 weeks. Forty percent were early-onset, less than 2 years; 37% were 2 to 12 years, and 24% were adult-onset or over 12 years. At baseline, 42% of the treatment cohort could walk, half of them were on ventilators and 21% were on feeding tubes. The treatment effects were compared to 68 untreated patients and they looked at motor, respiratory and feeding, and they compared it with the patients' own pretreatment status. What they found was treatment was well-tolerated, safe, and effective at improving or stabilizing TK2 deficiency. Remember, this is a relentlessly progressive condition.

In the early-onset group, 73% of the patients improved and 27% of them remained stable. If you add that number together, that's 100%. No one got worse while they were taking this therapy, no one declined. The natural history is decline. So, this treatment worked for everyone. In the mid-onset group, 79% improved and 21% remained stable. Again, everyone at least maintained. In the late-onset group, 44% improved and 33% remained stable. Some people were able to regain previously lost milestones. Three patients who had lost the ability to walk regained the ability to walk. One patient who never walked started walking. One patient who was on 24-hour-a-day mechanical ventilation discontinued all of their respiratory support. And 3 of the 8 patients on feeding tubes had their feeding tubes removed.

There are adverse events. Ninety-five percent of patients had adverse events, mostly diarrhea, a few lab abnormalities. But no one died. Again, the fact that no one died is shocking and very significant in this population of patients with TK2 deficiency.

Key Takeaways

Mitochondrial diseases can be caused by nuclear genes and TK2 deficiency can present in late teens or adults. Myopathy is not a diagnosis, so we need to keep looking until we get that diagnosis. Genetic testing is indicated early in the diagnostic process where a mitochondrial disease is suspected. And MT1621 is a new therapy, still under investigation, but it does correct the problem caused by TK2 deficiency and it improves the symptoms. So, this again is why it is really important, 1, to get the diagnosis and, 2, to refer your patients somewhere where they can potentially get on this therapy if you find one.

Audience Questions

Q: You noted the difficulty managing patients who live some distance away. After all, there are few centers of excellence, they're geographically dispersed. So, can you comment on the role of other members of the healthcare team, particularly in the community settings, and their role in managing patients who have been diagnosed with mitochondrial disease?

A: The community members are the most important people in managing a patient with a mitochondrial disease. As I mentioned, the Mitochondrial Care Network was really designed to be a resource for local providers. So, we cannot manage the care of every patient with mitochondrial disease. What we can do is we can consult and provide recommendations. What I do at my center is, I will see a patient, I will assess their diagnosis among many types of mitochondrial disease, TK2D being one. I will assess their diagnosis, I will

determine what clinical trials they might be eligible for, what therapies I think might be appropriate. I will make those recommendations back to their local provider and I will then work with their local provider to help them access whatever care they might need. So, it is essential for the local provider to maintain the primary control of taking care of that patient because we cannot do it from afar. That patient needs a good local provider that they know and trust, who they can see, who can work with the mitochondrial care physician to help take care of that patient. Therefore, we see ourselves as just a resource.

Q: Are there other conditions that display considerable phenotypic overlap with mitochondrial disease? And, if there are, what are they?

A: There are so many conditions that display phenotypic overlap with mitochondrial disease, yeah, and that's why I say it's so hard to tease it out. So, years ago when I started doing this, mitochondrial disease was mostly diagnosed by muscle biopsy and, as the genetic testing became more and more available, we started doing more and more genetic testing on our patients who had been clinically diagnosed with mitochondrial disease. It's so interesting to see how many of the patients that we initially though had a genetic mitochondrial disease ended up with something else. One of the common examples that we use is Rett Syndrome, MECP2, especially atypical Rett Syndrome. So, the MECP2 mutations very commonly present looking a lot like a mitochondrial disease, especially early in the course and especially if they're not classic Rett phenotype. So, I could give you a list of 200 diseases that can look like a mitochondrial disease which is why, again, I think genetic testing early in the course of your diagnostic work-up is important.

Q: To what degree do you find pediatric patients have seizures and encephalopathy? Is it as common as the other symptoms associated with early-onset TK2D?

A: Keep in mind that TK2D is very rare. It's considered one of the ultra-rare diseases. So, what I tell my patients with ultra-rare diseases is that if there's only 10 of you that we know about and something happens in 1 in 20 people, then we don't know about it yet. So, these are listed as 2 of the symptoms that can occur in patients with TK2D. I have never seen it in any of my patients and I have a few. But it has been seen in patients. There's always the question of how much of that could be related to things like nutritional deficits or hypoxia in patients who have respiratory issues or how much of that can be from electrolyte disturbances. So, I think whether or not it is a primary feature of the disease or whether it's secondary to something else, I'm not sure. I do believe it is more commonly seen in the infantile, early-onset group than the later-onset patients.

Q: Is bulbar weakness seen exclusively in adults with late-onset or can it be observed in the other 2 presentations?

A: It should be observed in the other 2 presentations. I believe it's a later onset symptom in the disease course. What you notice if you really dive deep into these 3 phenotypic presentations is that a lot of the adult-onset symptoms are more mild symptoms of the early-onset. And as they're more mild the patients tend to live a lot longer and so you tend to see more symptoms arising. So, things like the bulbar weakness, I think, is really just a progression of the weakness that you don't ever see in the younger population because, unfortunately, they pass away before they're able to develop the bulbar weakness. It's like why don't we see the dysarthria in the early-onset—because they never learn to talk. So, it would probably be there if they talked, but they never get to a point where they can talk so they're never dysarthric. So, I believe the bulbar symptoms are probably there in the early-onset, we just don't see them.

Q: If you have an adult female who has exhibited myopathy off and on for years but has managed to cope with her setbacks, would you still recommend genetic testing for this patient?

A: I absolutely would. That's actually the patient that I would recommend it for because my concern is what if she has something like this and she's on her way to getting worse. And I see a lot of older adults who have had myopathy for many years who, all of a sudden, something happens like they have to have surgery and it causes a progression of their disease and we didn't know, and all of a sudden, we don't know what they have. Knowledge is power and knowing what they have can help plan for and predict whether or not they need to be careful, or whether or not there is some sort of an expectation they may develop a problem later on.

Q: This should be another example of a patient where you would test them. You talked earlier about a patient who had genetic testing several years ago, maybe it was negative, but now you would suggest, due to advances in testing,

that they be tested. So, this actually is a catchment, not just early on in the diagnosis.

A: Right. I would do whole-exome on that patient and just see what you get.

Q: Are there resources available for patients diagnosed with TK2D that you'd recommend they could access?

A: Yes, so there are 2 nonprofit organizations that are very active in providing support for mitochondrial patients in general. One of them is called the United Mitochondrial Disease Foundation and the other one is called MitoAction. You can Google either one of those and both of them, again, are patient advocacy groups that would be able to point you to a whole slew of resources for patients with TK2 deficiency.

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