Transcript Details
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Mitochondrial Matters: A Clinician's Insights on Thymidine Kinase 2 Deficiency

Announcer:
Welcome to *NeuroFrontiers* on ReachMD. On this episode, supported by UCB, we'll examine the disease burden for patients with thymidine kinase 2 deficiency, or TK2d for short, with Dr. Bruce Cohen. Not only is Dr. Cohen a Pediatric Neurologist and the Chair of the NeuroDevelopmental Science Center at Akron Children's Hospital but he's also considered one of the world's leading experts in mitochondrial diseases. Here he is now.

Dr. Cohen:
There are several unmet needs of patients with thymidine kinase 2 deficiency. Let me go through these one by one. First of all, this is a very rare disorder. The manifestations of this disorder are well described in literature but are rather nonspecific and blend in with clinical manifestations of other neuromuscular and encephalopathic disorders. It's also difficult to diagnose this because there's no single age range that patients can present. Patients with TK2 deficiency can present anywhere between infancy and mid-adult life. And although the clinical manifestations are more severe in infancy than they are in older childhood or mid-adult life, it remains very difficult to use age as a cutoff factor for thinking about TK2 deficiency.

Mutations in the TK2 gene result in dysfunction of the thymidine kinase protein, which results in altered thymidine levels within the mitochondria. This ends up decreasing the synthesis and fidelity of the mitochondrial DNA replication cycle, resulting in mitochondrial DNA depletion over time. And this depletion leads to mitochondrial failure and the clinical manifestations of TK2 deficiency.

The disease manifestations appear similar to other rare disorders, and some not-so-rare disorders, which we'll discuss later. In addition, there is no specific biomarker for TK2 deficiency. The only way to make a definitive diagnosis of TK2 deficiency is with genetic testing. This is best performed on a platform that screens for dozens, if not hundreds, of mitochondrial genes and neuromuscular genes or the use of whole exome genomic sequencing or whole genome sequencing.

At this time, the only treatment includes supportive therapy, and although this is helpful, it is not curative for the disease itself. Although there are treatments on the horizon, these still are in the future. Right now, there are no approved therapies specific for TK2d. When discussing TK2d, it's important to consider the different manifestations of how patients present, and then develop a care plan around those manifestations.

One of the hallmark features of TK2 disease at any stage of presentation is myopathy, muscle weakness. This is universal and profound in infants. In addition to this profound myopathy that's universal in infancy, patients can have an encephalopathy. And in fact, even brain malformation disorders, such as lissencephaly, have been reported, suggesting that disease onset is prenatal in those patients.

There are also extra neurologic manifestations of TK2d in some infants. This includes bone disorders, cardiomyopathy, cardiac conduction defects GI dysmotility, hepatopathy, and nephropathy as well. All these things need to be looked for in screening patients identified with TK2d if they haven't been identified already in the evaluation.

The disease manifestations in younger children include myopathy and include some of the manifestations on occasion that I described in the infancy. The adolescent and adult-onset disease is manifested by a myopathy but seems to be centered not only along the axial component of the body but mainly the head and neck.

There's a biomarker, called GDF-15, growth differentiating factor-15. This is a commercially available biomarker and is elevated massively in the infant onset, and less so but quite elevated in childhood onset and adult onset as well. This biomarker has been linked to mitochondrial myopathy of many types, not just TK2d. But if it is elevated, it sends you down the pathway that you need to investigate

further.

I think the most important aspect of care in patients with TKd deficiency is developing a care team that meets all the needs of the patient. This has to be a multidisciplinary team. The neurologist would be the person addressing some of the manifestations of TK2d, especially the myopathic manifestations, but would also include the use of physical medicine and a rehabilitation physician or a physiatrist to help meet the day-to-day ADL issues that come up in patients with TK2d. The use of an ophthalmologist trained in the diagnosis and treatment of progressive external ophthalmoplegia is necessary, and of course, variable depending on the clinical manifestations of the disease. In addition to the physiatrist, any patient with swallowing difficulties or ventilatory difficulties needs to be cared for by an expert, such as a pulmonologist, and consider the use of noninvasive ventilatory support, such as BiPaP or invasive ventilatory support, such as a tracheostomy and ventilation. Because gastrointestinal manifestations are common in TK2 deficiency, especially in the infants, there needs to be a gastroenterologist and a nutritionist involved in the patient's care. Any patient with identified cardiac conduction defects or cardiomyopathy needs to be cared for by a cardiologist.

Announcer:
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