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Uncovering the Disease Burden of Untreated Pediatric TK2 Deficiency

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

Dr. Turck:
This is *Clinician's Roundtable* on ReachMD, and I'm Dr. Charles Turck. Joining me to share findings on the disease course in thymidine kinase 2 deficiency, or TK2d for short, in untreated children is Dr. Cristina Dominguez-Gonzalez. She's a physician in the Department of Neurology at the University Hospital 12 de Octubre in Madrid. Dr. Dominguez-Gonzalez, welcome to the program.

Dr. Dominguez-Gonzalez:
Hello. Thanks for having me.

Dr. Turck:
So let's start with a bit of background, Dr. Dominguez-Gonzalez. Why is it so important to understand the natural history of TK2d in pediatric patients?

Dr. Dominguez-Gonzalez:
Well, understanding the natural history of TK2d is essential to define the full clinical spectrum and progression of this ultra-rare mitochondrial disease. The early-onset forms typically progress rapidly to severe morbidity and mortality, yet no approved disease-modifying treatments currently exist. In addition, TK2d is often underdiagnosed and misdiagnosed. And available data on its natural course have been historically limited.

By focusing on untreated patients with symptom onset before the age of 12—a group known to experience the highest disease burden—this study provides critical baseline information for recognizing disease trajectories, guiding patient management, and supporting the design of future therapeutic trials.

Dr. Turck:
Now, as I understand it, this study leveraged the comprehensive disease course dataset, which pooled data from clinical trials, retrospective chart reviews, other literature reviews, and expanded access programs to create the largest international dataset of untreated patients with TK2d. From your perspective, what makes this kind of design so meaningful, especially in a rare disease setting?

Dr. Dominguez-Gonzalez:
Well, this dataset included 199 patients with symptom onset before the age of 12, and that represents almost all patients currently known. So we were able to combine data from the literature review and also the pre-treatment period of patients that received treatment afterward. And with that, this is a huge international cohort that allows us to have an overview of the disease progression before any therapeutic intervention.

I think that this level of data aggregation is exceptional for an ultra-rare disorder, and this is the best way to establish the meaningful baselines for survival, milestone loss, and supportive care needs for these patients.

Dr. Turck:
Now, with all of that in mind, let's turn to the results. The data showed that over half of untreated pediatric patients with TK2d had died by a median age of just 1.9 years, and the estimated median survival from symptom onset was only 2.6 years. What do these outcomes tell us about how the disease progresses?

Dr. Dominguez-Gonzalez:
Well, these findings underscore the rapid and very severe progression of TK2 deficiency in the early-onset cases. The data demonstrate that more than half of the untreated pediatric patients die before the age of 2, with a median survival of only 2.6 years from symptom onset. So the disease has very high mortality, which highlights the urgent need for early recognition first and then for the development of new treatments and interventions that are able to treat or modify the natural history of disease.

Dr. Turck:
For those just tuning in, you're listening to *Clinician's Roundtable* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Cristina Dominguez-Gonzalez about her research on disease progression in pediatric-onset TK2d, or thymidine kinase 2 deficiency.

So let's continue to take a closer look at the findings, Dr. Dominguez-Gonzalez. Among patients who, in life, initially achieved a motor milestone like standing or walking unassisted, more than 80 percent later lost those abilities, and nearly 40 percent lost four or more milestones. How do you interpret the significance of this functional decline, particularly in terms of disease burden and quality of life?

Dr. Dominguez-Gonzalez:
The loss of developmental motor milestones represents the major indicator of disease burden and its quality-of-life impact because the loss of previously acquired abilities, such as walking unassisted, profoundly affects daily functioning and independence. The high frequency of milestone loss—over 80 percent of the patients lost one motor milestone, and 40 percent of them lost four or more abilities—highlights the aggressive and the progressive nature of TK2 deficiency. And these patients generally first develop normally, and then they lost their motor abilities afterward. So this data further emphasized the critical need for early diagnosis, as we said before, when we were talking about survival.

Dr. Turck:
Now, the study also found that 41 percent of patients required ventilatory support, and 14 percent required feeding tube support, often several years after symptom onset. Would you tell us what these findings mean for long-term care and disease planning?

Dr. Dominguez-Gonzalez:
These findings highlight the substantial long-term care that is needed in patients with TK2 deficiency. Respiratory insufficiency is the main cause of morbidity and mortality in patients with early-onset TK2 deficiency, and therefore, the requirement of this ventilatory and feeding tube support reflects the significant respiratory and nutritional compromise that often develops after the onset of the motor decline.

The disease trajectory underscores the importance of proactive and multidisciplinary management to address these evolving medical needs. And in particular, patients with TK2d will need pulmonologists from the time of diagnosis to prevent complications and to treat the probable respiratory insufficiency that will appear soon after their disease onset.

Dr. Turck:
And if we look at the broader implications of these findings before we close, Dr. Dominguez-Gonzalez, how might they inform future care models or clinical trials for TK2d?

Dr. Dominguez-Gonzalez:
These findings have important implications for both clinical management and future trial design in this disease. This dataset provides the most comprehensive view to date of disease burden in untreated pediatric patients, establishing essential baseline comparators for upcoming clinical studies. These results reinforce the critical need for an early diagnosis, multidisciplinary supportive care, and accelerated efforts to develop disease-modifying therapies. Moreover, because loss of motor milestones is rarely reversible, timely therapeutic intervention may be key to preserving function and improving long-term outcomes.

Dr. Turck:
Well, with those implications in mind, I want to thank my guest, Dr. Cristina Dominguez-Gonzalez, for joining me to discuss the disease course of thymidine kinase 2 deficiency in untreated pediatric patients. Dr. Dominguez-Gonzalez, it was great having you on the program.

Dr. Dominguez-Gonzalez:
Thank you.

Announcer:
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