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Untreated Thymidine Kinase 2 Deficiency: Mapping the Progressive Disease Course

Ryan Quigley:

You're listening to ReachMD, and this is an *AudioAbstract*. I'm Ryan Quigley, and today, I'll be discussing a large natural history study of untreated thymidine kinase 2 deficiency, published in *Brain Communications* in 2026.

Thymidine kinase 2 deficiency, also known as TK2d, is an ultra-rare genetic mitochondrial disease marked by progressive, debilitating muscle weakness and respiratory insufficiency, with an increased risk of early death. Because TK2d is so rare, data describing its natural history and untreated disease course remain limited. Until recently, management was limited to supportive care, so understanding the untreated disease course and disease burden on patients is important context, both for clinical care and for evaluating emerging therapies.

Because of that, Domínguez-González and colleagues assembled one of the largest international datasets of thymidine kinase 2 deficiency to date. They combined published cases and retrospective chart-review data with pretreatment observations from clinical studies and expanded-access programs. All patients had genetically confirmed disease.

The final dataset included 257 patients. 199 developed symptoms by age 12. Another 49 had onset after age 12, and onset age was unavailable for nine patients. The investigators examined survival, developmental motor milestones, and the need for ventilatory and feeding support.

The survival findings highlight how strongly disease course varies with age at symptom onset. Over half of the patients with TK2d onset by age 12 died, with a median age at death of about two years. In comparison, 22.2 percent of patients whose symptoms began after age 12 died, with a median age at death of 64 years.

Most patients started to lose developmental motor milestones within the first few years of symptom onset, progressing from loss of running and stair-climbing abilities to walking, standing, sitting, and ultimately head control. Among earlier-onset patients with adequate milestone data, about eight out of 10 lost at least one previously acquired motor milestone. More than a third lost four or more. The median age at first milestone loss was only two years.

And once motor function was lost, recovery was uncommon. Among 71 patients who lost at least one milestone, only three spontaneously regained one. That's about four percent. The overall pattern therefore points toward steady, largely irreversible progression.

Later-onset TK2d disease progressed more slowly, but it wasn't benign. Among patients with onset after age 12 and available data, about one-third lost at least one motor milestone. Running, climbing stairs without assistance, and independent walking were among the functions affected.

Respiratory involvement added another major dimension to disease burden. Ventilatory support was reported in about 41 percent of patients with symptom onset by age 12 and 47 percent of those with later onset. Because ventilation data were missing for a sizable share of patients, the authors note that actual use is likely underreported. Earlier-onset patients began ventilation at a median age of three years. Among those with available information on daily use, support was often needed for substantial portions of the day.

Feeding support was also required, although these data were also incomplete. Feeding tubes were reported in 14 percent of earlier-onset patients and eight percent of later-onset patients. Dysphagia was a common reason for tube placement.

There are important limitations to keep in mind. This dataset pooled retrospective and prospective information from several sources, so outcomes weren't collected uniformly. Missing data was substantial for some measures, including on motor milestones and feeding

support. The pretreatment clinical-study population was also excluded from the survival analysis to avoid immortal-time bias. And because treatment eligibility can select for particular patients, the functional analyses may still be affected by selection bias.

Taken together, these findings characterize TK2d as a relentlessly progressive disorder across ages of onset, with the greatest burden in patients who develop symptoms earlier in life. The data also provide a clearer benchmark for counseling families, monitoring progression, and interpreting outcomes from therapeutic studies. Perhaps most importantly, they quantify how quickly meaningful functions can be lost, and how rarely those losses reverse spontaneously.

This has been an *AudioAbstract*, and I'm Ryan Quigley. To access this and other episodes in our series, visit ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

Reference:

Domínguez-González C, Garone C, Nascimento A, et al. Disease burden of untreated thymidine kinase 2 deficiency: insights from a large patient dataset. *Brain Commun.* 2026;8(3):fcag200. doi:10.1093/braincomms/fcag200