

Patients' lived experience of thymidine kinase 2 deficiency (TK2d): results from the Assessment of TK2d Patient Perspectives (ATP) study

16th European Paediatric Neurology Society (EPNS) Congress; Munich, Germany; 8–12 July 2025

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, genetic, life-threatening, mitochondrial disease that severely impacts daily living and health-related quality of life (HRQoL)¹
- TK2d leads to mitochondrial DNA depletion and/or deletions and is associated with progressive proximal myopathy affecting motor function, breathing and feeding, and with premature death²
- Age of TK2d symptom onset (AoO) has a profound impact on disease course, with early-onset disease typically associated with more rapid and severe disease progression^{3–4}
- There is currently no approved treatment for TK2d; however, a pyrimidine nucleoside therapy is in development⁵
- While previous research suggests an immense patient burden associated with TK2d,^{4,6} the lived experience, crucial for characterizing the disease burden and for tailoring management, remains poorly understood

Objective

- To explore patients' lived experience of TK2d and the impact of the disease on patients' HRQoL

Methods

Study design

- The cross-sectional Assessment of TK2d Patient Perspectives (ATP) study was co-developed with a steering committee of patient and clinical advisors to assist with planning, development and execution of the study
- The study consisted of a mixed-methods online survey including multiple-choice and open-text questions, and numerical and verbal rating scales
- A central US Institutional Review Board waiver was obtained; all participants provided informed consent
- Global mitochondrial disease patient groups invited patients and caregivers to complete the survey between September 2023 and February 2024

Population

- The study captured patient and caregiver experiences; a subset of data on the impact of TK2d on patients is presented here
- Patients, or caregivers of patients answering on behalf of patients, aged ≥18 years with a self-reported, genetically confirmed TK2d diagnosis were included
- Patients with TK2d who had received nucleoside treatment in a clinical trial were excluded

Data analysis

- Quantitative analysis was performed using Stata v18 software⁷ for Windows
- Qualitative analysis was performed using inductive thematic analysis⁸ and content analysis when appropriate
- Primary data presented here are stratified by developmental age group at time of survey completion (infant, 0–2 years; child, 3–15 years; young adult, 16–34 years; adult, ≥35 years); AoO is stratified as ≤2 years, >2 to ≤12 years and >12 years

Results

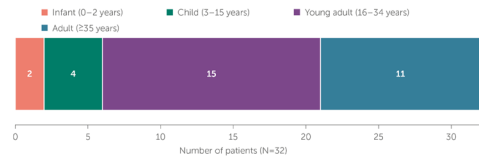
Patient demographics

- Thirty-two responses (24 patient self-reports; 6 proxy reports by caregivers; 2 proxy reports by bereaved caregivers) were obtained
- Median (range) patient age at time of survey/at death was 30.5 (1–54) years
 - Most patients were aged ≥16 years (Figure 1)
- AoO was ≤2 years (n=12), >2 to ≤12 years (n=10) or >12 years (n=10)
- Respondents were from 12 countries across North America (n=15), Europe (n=11) and the rest of the world (n=6)

Clinical characteristics

- Patients had been living with symptoms of TK2d for a median (range) of 18 (1–45) years
- Eight patients were receiving or had previously received pyrimidine nucleoside therapy; six patients were receiving treatment via a compassionate use program at the time of survey completion, one patient had received treatment in the past and one deceased patient had previously received treatment

Figure 1. Number of respondents by age group



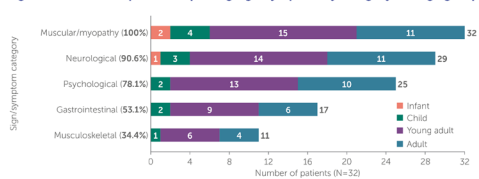
Functional status

- Three patients were able to complete normal activities with little impact from TK2d (one child and two young adults)
- Twenty-five patients needed home modifications and support to help with daily activities, including nine who required full-time support
- Four patients required full-time medical support

Signs and symptoms of TK2d

- Patients carried a heavy burden of signs and symptoms in multiple body systems regardless of their age (Figure 2)
- Many patients reported signs and symptoms beyond the characteristic myopathy/muscle weakness associated with TK2d

Figure 2. Number of patients reporting sign/symptom by category and age group

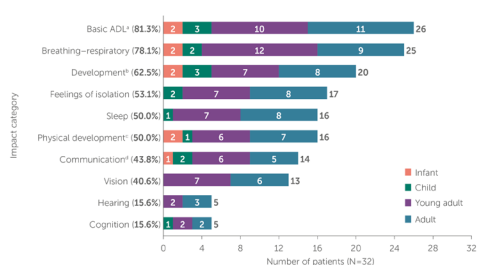


Signs and symptoms included in each category – **muscular/myopathy**: proximal muscle weakness and fatigue, bulbar and facial, respiratory, ocular; **neurological**: poor coordination or balance, seizures, heat intolerance, pain or discomfort; **psychological**: anxiety, depression, mood swings, irritability; **gastrointestinal**: frequent sickness, nausea or vomiting, frequent constipation, frequent diarrhea; **musculoskeletal**: joint stiffness, frequent bone fractures.

Impacts of TK2d

- Patients' symptoms affected multiple aspects of their physical and mental well-being (Figure 3)

Figure 3. Number of patients experiencing impact by impact category and age group



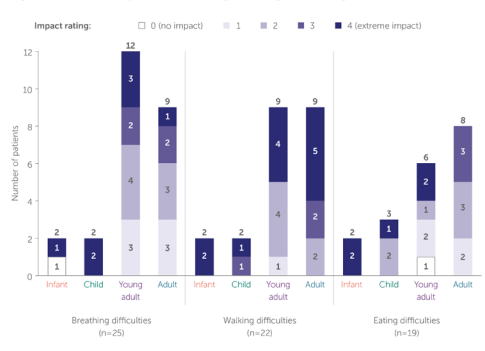
Impacts are grouped by World Health Organization International Classification of Functioning, Disability and Health components – impairment, activity and participation. *Basic ADL, include difficulties walking and eating/swallowing, issues with control of urine and issues with bowel control. †Development include developmental delays and loss of normal milestones and/or functions. ‡Physical development includes failure to thrive, losing weight or unable to maintain weight, and malnutrition. *Communication includes communication challenges, problems with non-verbal communication (e.g. nodding) and speech problems.

ADL, activities of daily living

"It is difficult to see my physical strength diminish and feel like I am losing independence. There are normal day-to-day activities that require extra planning and it's overwhelming."
– Young adult, AoO >2 to ≤12 years (self-report)

- The three most commonly reported signs/symptoms and impacts that respondents selected as affecting their daily lives the most were difficulties with lower body muscle weakness/walking, breathing and fatigue
- Using a rating scale from 0 (no impact) to 4 (extreme impact), patients provided additional information regarding their experience of three areas of functioning known to be impacted by TK2d (Figure 4; Table 1)

Figure 4. Level of impact of breathing, walking and eating difficulties on HRQoL



Data on the level of impact of breathing, walking and eating difficulties on HRQoL were only available for patients who reported HRQoL, health-related quality of life.

Table 1. Patients affected by breathing, walking and eating/swallowing difficulties with example quotes

Breathing difficulties (n=25, 78.1%) <i>"[Child's name] was invasively ventilated aged 1 year 3 months, he was in intensive care on life support for 5 weeks, extubated 3 times, eventually he could survive on CPAP but this meant we had to live in hospital for the rest of his short life, attached to the machine."</i> – Infant (d), AoO ≤2 years (proxy bereaved caregiver) <i>"Daily life attached to a breathing ventilator makes showering, using the bathroom and eating difficult. My life has become sedentary due to the use of the breathing ventilator."</i> – Adult, AoO >12 years (self-report)	Walking difficulties (n=22, 68.8%) <i>"It limits literally everything you do all day from going to the bathroom to cooking or working."</i> – Young adult, AoO >2 to ≤12 years (self-report) <i>"Wanting to walk like I used to and not being able to as I tire really quickly. It makes my legs really hurt to the point I have to sit down because I feel so weak, not being able to do lots of things at home and needing to ask for help, not being able to climb the stairs"</i> – Adult, AoO >12 years (self-report)	Eating/swallowing difficulties (n=19, 59.4%) <i>"I feed through a feeding tube four times a day. It's hard to go out when you can't eat somewhere, so I can only do it at home."</i> – Young adult, AoO ≤2 years (self-report) <i>"My daily life at meals has been impacted since I started to experience weakness in my swallowing. I no longer enjoy mealtimes or going out to eat as much as I did before. There are times that I would rather stop eating to avoid exhausting myself during a meal."</i> – Adult, AoO >12 years (self-report)
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"I feed through a feeding tube four times a day. It's hard to go out when you can't eat somewhere, so I can only do it at home." – Young adult, AoO ≤2 years (self-report)

AoO, age of TK2d symptom onset; CPAP, continuous positive airway pressure; d, deceased.

Lived experience

- When patients were asked to use some words to describe their experience of living with TK2d, 'exhaustion' was the word most frequently used

"Living with TK2d isn't easy. It's daily survival and coping with extreme tiredness, difficulty breathing, swallowing and speaking, depending on other people, depending on a non-invasive respirator, routine daily care and home care, coping with emotions day to day, all the while being hopeful of better days ahead."
– Adult, AoO ≤2 years (self-report)

- Patients lost their independence as the loss of function progressed, making them more reliant on others and medical equipment
- For example, of the 27 patients queried about their ability to perform household tasks inside the home, 20 patients (74.1%) reported needing support, with a further 6 patients (22.2%) reporting being unable to perform these tasks at all
- The most common themes from the analysis of lived experience responses are summarized in Figure 5

Figure 5. Common themes: most challenging aspects of living with TK2d



AoO, age of TK2d symptom onset; TK2d, thymidine kinase 2 deficiency.

Impact on HRQoL domains

- The impacts of TK2d on patients' HRQoL were substantial across all ages and AoO, with negative impacts reported across all domains (Figure 6)
- Negative impacts were associated with reliance on medical equipment and higher support needs
- Positive impacts reported by patients included feelings of gratitude, personal growth, increased connection to community and hope for new treatments

"My diagnosis has allowed me to connect with others and see things from a perspective I did not have before. There's things I took for granted before. And there's handicap parking. Guess we can call that a perk." – Young adult, AoO >2 to ≤12 years (self-report)

Conclusions and Outlook



The lived experiences shared by patients of all ages illustrate that TK2d imposes a substantial burden, marked by debilitating physical impacts and severe psychological strain, which profoundly affect daily functioning and overall well-being

Walking, breathing and eating/swallowing difficulties had an 'extreme' impact on HRQoL, with a progressive impact on patients' ability to be independent in their daily lives



Impacts were substantial regardless of age group and age of TK2d symptom onset

Breathing difficulties were reported as impactful by all age groups; difficulties with motor functions and milestone developments were reported in infants, whereas adults and young adults rated lower body muscle weakness and anxiety as highly impactful



These findings, along with clinical insights, provide a more comprehensive understanding of disease impact and may facilitate the development of improved treatment options and supportive strategies for those living with TK2d

Figure 6. Summary of patient ratings of impact of TK2d on HRQoL domains



Patients reporting somewhat positive or extremely positive impacts in each HRQoL domain were as follows: mood, 9.4% (n=3); relationships with friends, 3.8% (n=1); relationships with partner/spouse or family, 25.0% (n=8); social and leisure activities, 12.5% (n=4); finances, 3.8% (n=1); education or employment, 6.7% (n=2).

*Excludes infants and children.

HRQoL, health-related quality of life; TK2d, thymidine kinase 2 deficiency.

This poster was previously presented at 2025 Molecular Sympathy Association (MOSA) Clinical & Scientific Conference, 16–18 March 2025, Dallas, TX, USA. **Acknowledgements:** This study was funded by UCB. The authors acknowledge Clinical Pharmacology, Clinical, US, for writing and editorial assistance which was funded by UCB, in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.medicines.org.uk/guidance/good-publication-practice-2022). The authors also thank the patients and caregivers who took part in the study and the patient advocates for their support of the study. **References:** 1. Smeets J, et al. *Neurology* 2023;101:12. 2. Smeets J, et al. *Neurology* 2023;101:12. 3. Smeets J, et al. *Neurology* 2023;101:12. 4. Wang J, et al. *Neurology* 2023;101:12. 5. Smeets J, et al. *Neurology* 2023;101:12. 6. Smeets J, et al. *Neurology* 2023;101:12. 7. Smeets J, et al. *Neurology* 2023;101:12. 8. Smeets J, et al. *Neurology* 2023;101:12. 9. 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