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Patient experiences of thymidine kinase 2 deficiency (TK2d): preliminary results from an online survey conducted in partnership with the patient community

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal recessive mitochondrial disease associated with progressive, life-threatening myopathy that severely affects patients' quality of life[1,2]
  - TK2d affects all aspects of life, and patients with TK2d may lose their ability to walk, to eat and to breathe independently[2]
  - The clinical manifestations of TK2d fall within a wide clinical spectrum; different subtypes have been reported based on the age at symptom onset and the timeline of disease progression[1,2]
  - Currently, there are no approved treatments for TK2d[3]
- Understanding the lived experience of patients and their caregivers is crucial for characterizing the burden of TK2d and tailoring disease management
  - To address this knowledge gap, the Assessment of TK2d Patient Perspectives (ATP) study was initiated in 2023 and is ongoing

Objective

- To present preliminary results on the lived experience of patients with TK2d as reported in the ATP study, and the impact of TK2d symptoms on health-related quality of life and activities of daily living

Methods

- The ATP study is a cross-sectional, mixed-methods study
  - An online survey was used to collect data from patients and caregivers
- The survey included multiple-choice, visual analog scales and open-text questions designed to capture the lived experience of patients with TK2d and their caregivers
  - This survey was co-created by study investigators and patient advisers[4]
    - Seven patient experts from the mitochondrial disease and TK2d patient community completed a pilot review of the survey and their feedback was incorporated into the final study survey
- These interim analyses include data collected from September 2023 to February 2024 and focus on questions related to the lived experiences from the patient perspective
  - Data from caregivers representing the patient are included but questions related to the caregiver perspective are excluded
- Patients were stratified according to age at symptom onset (≤2 years, >2 to 12 years or >12 years; self-reported) and age at the time of responding to the survey (infant [≤2 years], child [>2 to <18 years] or adult [≥18 years])

Recruitment

- Patients and caregivers of patients with a self-reported genetically confirmed diagnosis of TK2d were invited to complete the ATP survey by patient organizations and treating clinicians
- The survey was made available in the relevant language in countries where more than three patients with TK2d have been identified: Brazil (Portuguese), France (French), Germany (German), Italy (Italian), Mexico (Latin American Spanish), Spain (European Spanish), Turkey (Turkish), the UK (English) and the USA (English and Latin American Spanish)

Eligibility criteria

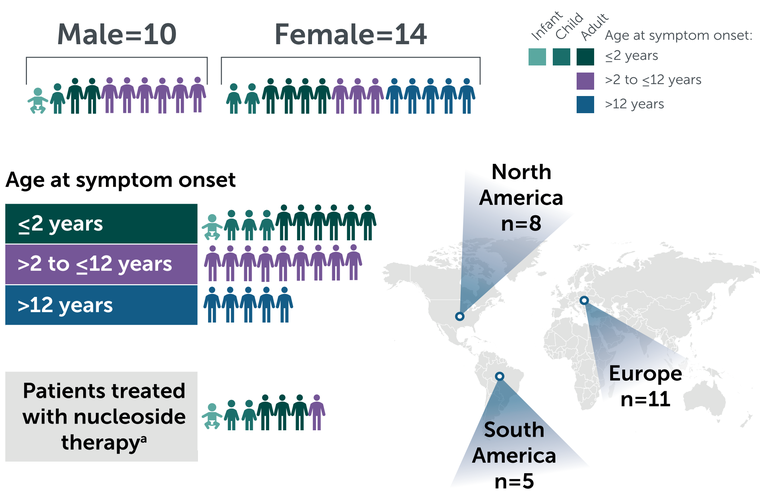
- To be eligible to complete the survey, the participants had to be:
  - aged 18 years or older
  - a person with or a caregiver of a person with a self-reported genetically confirmed diagnosis of TK2d
  - able to complete an online survey with minimal assistance and sufficient command of the language to read and to provide responses
- Patients with TK2d who had received nucleoside treatment in a clinical trial in the past or who were receiving it at the time of the study were excluded; patients treated with nucleoside treatment via a compassionate use program or other means were included

Results

Population

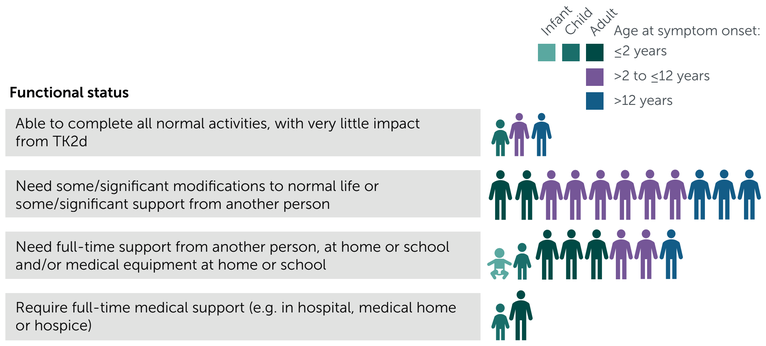
- In total, 24 patients with a median age of 31.0 years (mean [standard deviation]: 30.1 [13.63] years; range: 2–54 years) were included in the interim analysis; the demographics and clinical characteristics of this population are summarized in **Figure 1**
  - Most patients reported age of symptom onset ≤12 years (n=19)
  - Most patients were female (n=14) and were adults at the time of responding (n=20)
- Most patients completed the survey themselves (n=19), with the remaining answers provided by caregivers as the patient's proxy (n=5)
- At the time of responding, most patients required at least some assistance with daily activities (n=21), with 10 patients requiring full-time support (**Figure 2**)

Figure 1. Baseline demographics of patients in the interim analysis of the ATP study



[a]Of the 2 child respondents treated with nucleoside therapy with age of onset <2 years, 1 is currently receiving therapy, the other had used nucleoside therapy in the past but not now.
ATP, Assessment of TK2d Patient Perspectives.

Figure 2. Self-reported functional status of patients in the interim analysis of the ATP study

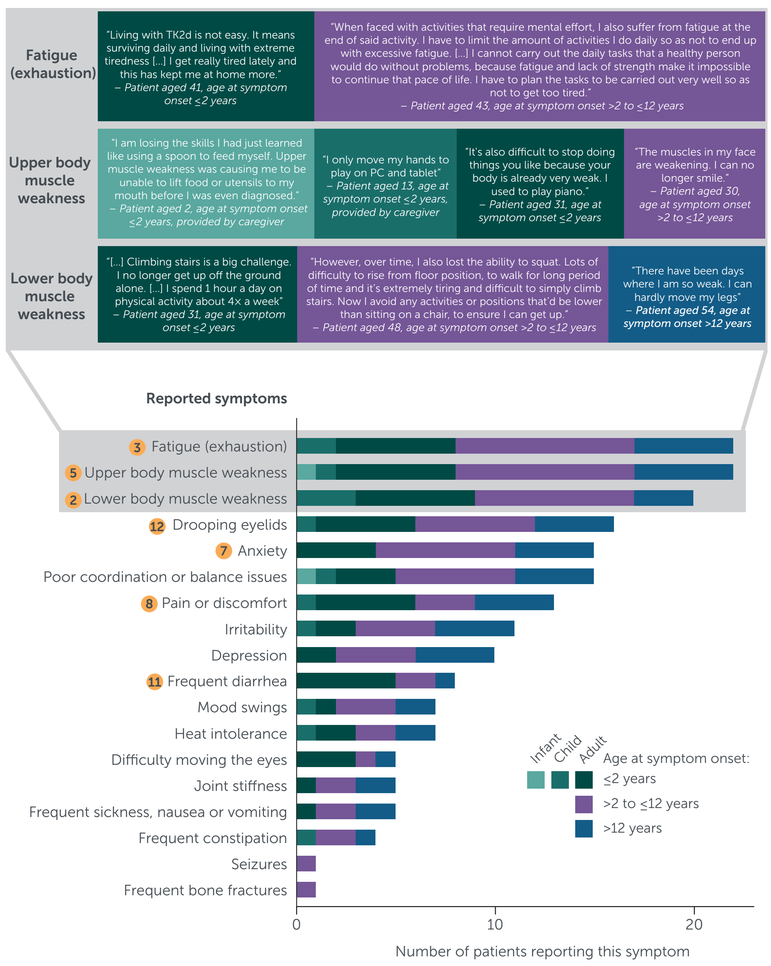


ATP, Assessment of TK2d Patient Perspectives.

Symptoms

- Patients in the ATP study reported experiencing a broad range of symptoms related to TK2d (**Figure 3**)
  - The most common symptoms were fatigue (91.7%), upper body weakness (91.7%) and lower body weakness (83.3%), consistent with the myopathic component of TK2d
  - Psychological symptoms were frequently reported, the most common being anxiety (62.5%), irritability (45.8%) and depression (41.7%)
    - The psychological burden was greatest for adult patients who first experienced TK2d symptoms at >12 years of age (n=5): all these patients reported psychological symptoms, with four reporting anxiety, depression and irritability, two reporting mood swings and one reporting feelings of isolation

Figure 3. Number of patients who reported experiencing each symptom, and quotes from patients illustrating their experiences of the most frequently reported symptoms



Yellow bubbles mark the top 13 most impactful experiences. When participants were asked to select the top 3, they considered both symptoms and impacts; the yellow bubble numbering therefore runs across **Figures 3** and **4**. Additional reported symptoms: muscle aches, burning and spasms, dizziness, tachycardia, dry and fatigued eyes, otitis, headaches, being unable to smile, sleep difficulties and feeling extremely cold.

Impact of TK2d on patients' lives

- Symptoms and signs of TK2d affected multiple aspects of patients' lives, ranging from their mental health to their communication or sleep (**Figure 4**)
  - The most common reported impacts were low energy levels (22/24), difficulty breathing (19/24) and difficulty walking (18/24)
- When asked about the three signs and symptoms that they found most impactful, patients and caregivers most commonly reported breathing problems, lower body muscle weakness and fatigue, with 57.9%, 40.0% and 31.8% of patients with those symptoms, respectively, reporting each as one of their top three most impactful signs and symptoms
  - The top 13 most impactful signs and symptoms are marked with a yellow bubble across **Figures 3** and **4**
- Specific words used by respondents to describe their experience of living with TK2d included exhausting, overwhelming, frustrating, difficult, challenging, debilitating, limiting, dependence and hopeless; additional words are captured in **Figure 5**
  - The degenerative nature of the condition was particularly challenging for patients who described experiencing emotional distress as their functional abilities and independence diminished

Figure 4. Number of patients reporting each impact of TK2d symptoms and quotes from patients about how TK2d affects their basic activities of daily living

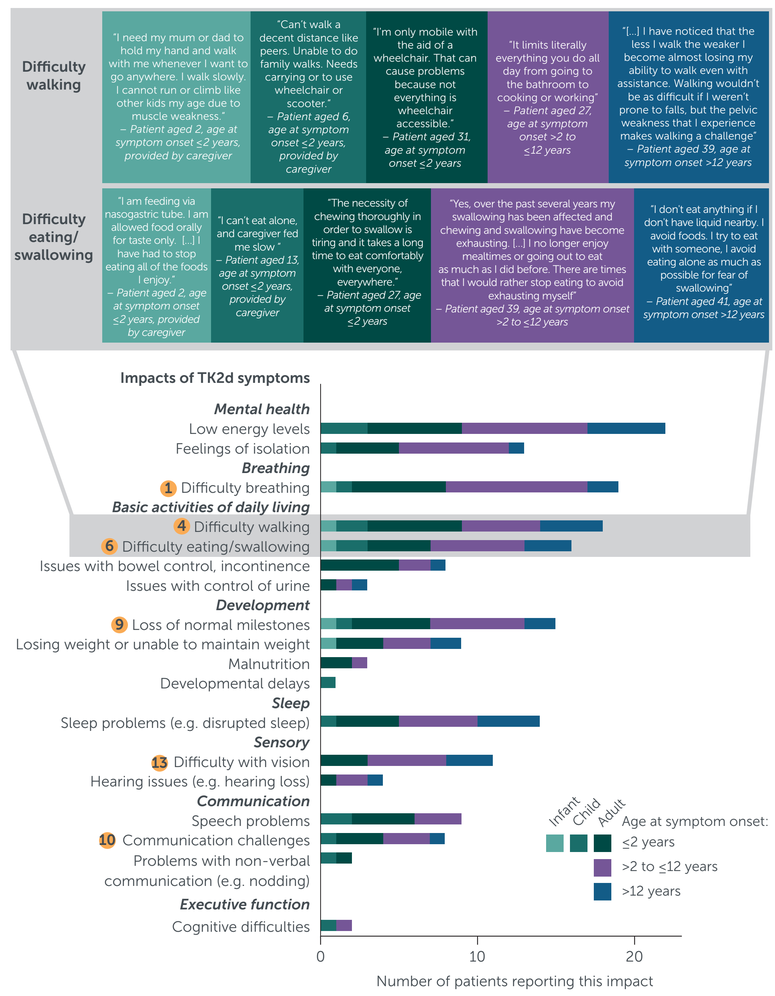


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Figure 5. Specific words and illustrative quotes used by respondents to describe their experiences

• Lack of energy • Frustration (not able to walk independently)	"I was learning to walk and at about 18 months started to lose this ability. I lost the ability to stand up and sit up by myself." – Patient aged 2, age at symptom onset ≤2 years, provided by caregiver
• Struggles (compared to peers) • Hope • Bedbound	"She is unaware why she struggles compared to peers. Sometimes says 'I'm stupid'." – Caregiver of a patient aged 6, age at symptom onset ≤2 years
• Fear • Frequent falls • Surviving • Acceptance • Early maturation • Exclusion • Uncertainty • Hope	"Being born with TK2d is like being born with a defective battery that at first works well but after a few months it begins to fail and your energy runs out faster, your body does not perform as it should, and over time it gets worse until one day the battery stops working completely." – Patient aged 31, age at symptom onset ≤2 years
• Failure • Embarrassment • Constant adaption • Isolating • Endurance • Self-hate • Cautious • Stressful • Pain • Fear of falling	"Adapting to a changing body as an adult is difficult. I met my partner, and we did so many things together and I always took pride in being independent. […] Asking for help has never been easy for me and having to do so now feels like defeat. […] This disease challenges my daily life and impacts all parts of my life in different ways." – Patient aged 30, age at symptom onset >2 to ≤12 years
• Pain • Depression • Helplessness	"Unsure what the future holds. Not sure how long it will be before I need a feeding tube, ventilator, or even a wheelchair." – Patient aged 39, age at symptom onset >12 years

Summary and Conclusions

This study highlights the unmet need and burden of disease in TK2d

- People with TK2d report a high burden of disease related to breathing difficulty, walking difficulty, muscle weakness, impact on energy levels, level of independence including for basic activities of daily living, and impacts on their mental health

The final results of the ATP study will provide valuable insights into the unmet needs and lived experience of patients with TK2d, and the impact on caregivers for patients with TK2d

Improved understanding of patients' and caregivers' experiences may empower patients and caregivers to seek support, inform decision-makers about medical needs and facilitate clinical pathways to improve the management of patients with TK2d

Next steps

- Recruitment for the study has been closed, and analyses of the final data set are ongoing, with results expected later this year
  - Results of these analyses will be submitted for publication in a peer-reviewed scientific journal
  - Findings will be shared with the global mitochondrial disease and TK2d patient community organizations who supported the development and recruitment of this study

Abbreviations: ATP, Assessment of TK2d Patient Perspectives; TK2d, thymidine kinase 2 deficiency.
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References: 1. Berardo A, *et al. J Neuromuscul Dis* 2022;9:225–35. 2. Garone C, *et al. J Med Genet* 2018;55:515–21. 3. de Barcelos IP, *et al. Curr Opin Neurol* 2019;32:715–21. 4. Balcells C, *et al.* Poster presented at the UMDF Symposium 2023, June 28–July 1, 2023, Charlotte, NC, USA.

Author disclosures: Cristy Balcells was an executive director of MitoAction (2006–2016), a consultant for Stealth BioTherapeutics (2016–2019) and the Barth Syndrome Foundation, a contractor for Zogenix Inc. and is an employee of UCB Pharma. Amel Karaa has received consultation fees from UCB Pharma. Katie Waller's organization has received fees from UCB Pharma for serving on a steering committee. Phil Yeske's organization has received fees from UCB Pharma for serving on a steering committee. Alexandra Morrison is an employee of Rare Disease Research Partners, providing professional research services to UCB Pharma. Marnie Ross is an employee of Rare Disease Research Partners, providing professional research services to UCB Pharma. Asha Hareendran is an employee and shareholder of UCB Pharma.