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Early symptoms and disease progression in thymidine kinase 2 deficiency: patient perspectives from an online forum

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal recessive, mitochondrial disease caused by pathogenic variants in the thymidine kinase 2 gene[1,2]
- TK2d is characterized by progressive, life-threatening proximal myopathy and impairment of motor function, breathing and feeding that severely affect daily living and health-related quality of life (HRQoL)[1–4]
  - Disease course varies by age of TK2d symptom onset (AoO), with earlier onset typically associated with more rapid and severe disease progression[5]
- Doxecitine and doxribtimine, an oral pyrimidine nucleoside therapy, is the first FDA- and EMA-approved treatment for adults and children with TK2d with AoO ≤12 years[6–8]
- Patient-reported perspectives in the global Assessment of TK2d Patient Perspectives (ATP) Part 1 illustrated, through a survey approach, the severe, progressive and cumulative impact of TK2d on HRQoL and independence[9,10]
- ATP Part 2 aimed, through a qualitative approach, to explore in more detail patient and caregiver perspectives on early symptoms and disease trajectory

Objective

- To explore patients' experiences of the early symptoms and progression of TK2d in depth

Methods

Study design

- ATP Part 2 was cross-sectional qualitative research consisting of an asynchronous online forum discussion available over a 6-week period (October 13–November 24, 2025)
- All project materials were codesigned with input from the study team and patient organizations
- Eligible participants who provided written informed consent completed a brief demographic and disease characteristic form and accessed the online forum to respond to moderators' questions on symptom onset, early disease progression and key events in the disease trajectory
  - In-forum translation was used to enable participants to contribute in their own language
- Here, we report findings on early TK2d symptoms and disease progression, as well as the associated impact on patients' physical and mental health

Population

- Study invitations were sent to 34/40 participants of ATP Part 1 (conducted 2023–2024) who had consented to be recontacted for future research
- Patients or proxy caregivers were required to be aged ≥18 years at the time of the study
- All included patients were required to have a self- or caregiver-reported genetically confirmed TK2d diagnosis
- Patients with TK2d who had received nucleoside treatment as part of a clinical trial were excluded; however, patients who received treatment via a compassionate use program were included

Data analysis

- Descriptive statistics were used to summarize patient demographics and disease characteristics
- Qualitative analysis of the forum discussions was performed using inductive thematic analysis[11] and results are presented in a narrative style

Results

Patient demographics and disease characteristics

- Of the 34 participants invited, 20 responded, and, of these, 10 (8 patients and 2 proxy caregivers) participated in ATP Part 2
- Patient demographics and disease characteristics are presented in **Table 1**

First symptoms of TK2d

- For most patients (8/10), the first symptoms were noticed in infancy (age ≤2 years; 5/10 patients) or childhood (age >2 to ≤12 years; 3/10 patients) (**Figure 1**)
  - These initial symptoms primarily involved lower and upper muscle weakness and included falls, difficulty getting up and 'floppiness'
- Physical limitations in childhood affected daily life and limited participation in family, social and school activities

Table 1. Patient characteristics

Characteristic		Patients (N=10)
Sex, female/male, n		7/3
Region, n	North, Central and South America	8
	Europe	2
Patient age at the time of the study	Median (min, max), years	36.0 (5.0, 56.4)
	<18 years, n	2[a]
	≥18 years, n	8
Patient age at TK2d symptom onset	Median (min, max), years	1.9 (0, 39.0)
	≤2 years, n	5
	>2 to ≤12 years, n	3
	>12 years, n	2
Age at TK2d diagnosis	Median (min, max), years	29.9 (3.0, 42.0)
	<18 years, n	3
	≥18 years, n	7
Currently receiving nucleoside therapy via compassionate use, n	No	2
	Yes	8
Time since initiating nucleoside therapy	n[b]	7
	Median (min, max), years	1.5 (1.2, 3.3)
Age at time of initiation of nucleoside therapy	n[b]	7
	Median (min, max), years	30.3 (3.1, 45.5)
Functional status, n	Able to complete all normal activities, with very little impact from TK2d	2
	Need some modifications to normal life or some support from another person	4
	Need significant support from another person, or adjustment to normal routines and activities	1
	Need full-time support from another person and medical equipment at home or school	3

[a]Reported by caregivers. [b]Missing data for one patient receiving nucleoside therapy.
max, maximum; min, minimum; TK2d, thymidine kinase 2 deficiency.

Data first presented at EuroMIT Conference 2026; Angers, France; May 31–June 4, 2026.

Figure 1. First symptoms reported by patients or their caregivers

	Infancy (≤2 years)	Childhood (>2 to ≤12 years)	Adolescence (>12 to <18 years)	Adulthood (≥18 years)
Onset of symptoms, n (%)	5/10	3/10	1/10	1/10
First symptoms: lower muscle weakness	• Frequent falls • Difficulty getting up from the ground	• Frequent falls • Unable to break falls with hand • Unable to get up themselves	–	• Difficulty climbing stairs
First symptoms: upper muscle weakness	• Hypotonia – Difficulty keeping neck steady – Head dropped down – Falling when sitting	• Can no longer lift a bottle • Can no longer raise arms above shoulder height • Unable to break falls with hands	–	• Arms easily tired when carrying baby
Additional first symptoms	• **Bulbar:** issues with swallowing and eating	• **Fatigue** • **Pain** in legs even at rest	• **Respiratory:** short of breath, more tired than others	• **Fatigue:** need to lie down regularly

Patient quote

> "*I don't remember it, but my mom has told me that when I started to walk, around the age of one, I fell a lot. She noticed that it wasn't normal, because it hadn't happened with my siblings.*"
> (Adult; AoO ≤2 years)

> "*Growing up I always thought I was weak and I used to compare myself to my cousins/siblings and school peers. […] I used to struggle with many physical activities such as running, throwing a ball, skipping the rope, jumping etc. I used to feel very tired by the time I used to go home from school.*"
> (Adult; AoO >2 to ≤12 years)

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

Initial consultations with healthcare professionals (HCPs)

- Early childhood symptoms, missed developmental milestones and comparisons with siblings prompted caregivers to seek medical help
- During initial consultations with HCPs, concerns were often dismissed, with HCPs considering symptoms to be normal, prescribing vitamins and/or recommending changes in diet

> "*I went to the [general practitioner] (GP) and the GP just brushed it off saying it's normal, nothing to be worried about. Around that time the most concerning symptom I used to struggle with was walking, climbing stairs and muscle pain.*" (Adult; AoO >2 to ≤12 years)

- Although respondents were not specifically asked to detail the number or type of HCP visited, visits to 18 different types of HCP were reported across all patients: primary care physicians, audiologists, hematologists, neurologists, cardiologists, epileptologists, gastroenterologists, geneticists, pediatricians, endocrinologists, ophthalmologists, otorhinolaryngologists (ear, nose and throat), orthopedists, pulmonologists, physiotherapists, speech therapists, nutritionists and urologists

> "*I have truly had every type of provider under the sun for most of my life.*"
> (Adult; AoO ≤2 years)

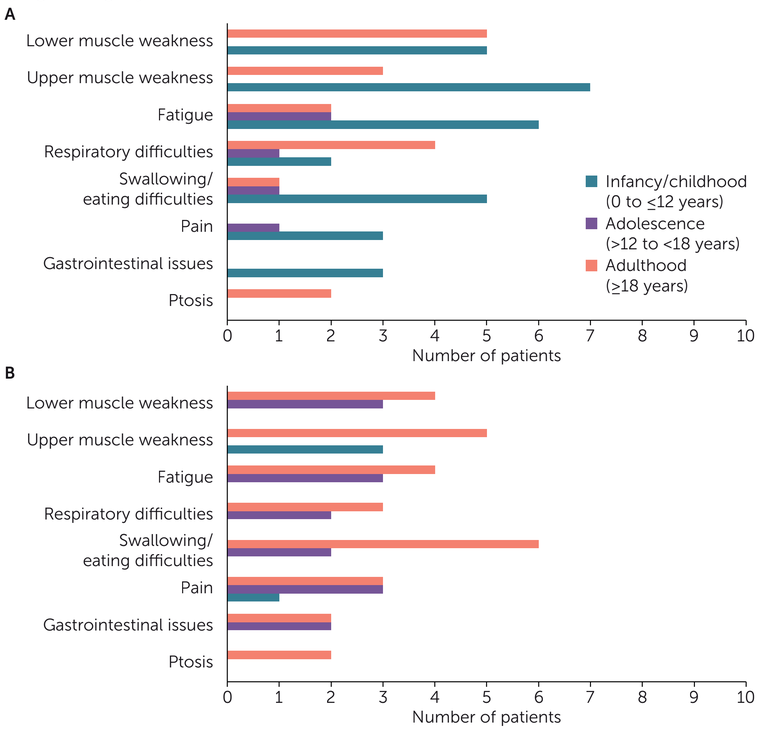
- Diagnosis of TK2d was usually prompted by a worsening of symptoms, TK2d being diagnosed in a sibling, patient's own research or chance (e.g. mention of symptoms at sibling's appointment)

Progression of TK2d and impact on daily life

- In addition to the progression of existing symptoms, new symptoms emerged and progressed in adolescence and adulthood, including respiratory difficulties, swallowing/feeding difficulties and fatigue, as well as muscle weakness (**Figure 2**)

> "*I was born with this disease, but it has progressed throughout my life, I believe. The muscle pain started in my teenage years and in adulthood there was greater respiratory and motor impairment.*"
> (Adult, AoO ≤2years)

Figure 2. Symptoms identified at (A) symptom onset and (B) symptom progression by age category



Conclusions and outlook

- For most patients, the first symptoms of TK2d emerged in infancy or early childhood and were related to muscle weakness, including respiratory and swallowing difficulties
- In adolescence and adulthood, disease progression and new symptoms (notably respiratory and swallowing difficulties) increasingly limited independence, driving greater need for assistive devices and caregiver support, disrupting education, employment and social participation, and worsening psychosocial well-being
- These findings highlight the initial symptoms, the signals of progression and the cumulative impacts of TK2d, underscoring the importance of early diagnosis to enable timely management of this disease

Figure 3. Impacts of symptom progression on physical and mental health

	Infancy/childhood (0 to ≤12 years)	Adolescence (>12 to <18 years)	Adulthood (≥18 years)
Impacts on physical health	• Difficulties in performing activities of daily life (e.g. dressing, bathing, cleaning teeth) • Unable to keep up with peers • Unable to play independently • **Adaptations:** mobility aids such as braces, bath chair, helmet	• Risk of falls – reluctance to take part in games and socialize • Unable to participate in school trips and long walks • Reduced participation in physical education • Some become dependent on others • **Adaptations:** request for ground floor classroom, increase in use of assistive breathing technology and mobility aids	• Unable to walk independently or at all • Unable to perform self-care activities or household chores • Increased reliance on assistive devices and mobility aids, and increased dependence on others • Reduced social life • Hospitalizations (for recurrent chest infections, pneumonia, bronchial aspiration) • **Adaptations:** wheelchair, tracheostomy, gastrostomy, breathing equipment (e.g. BiPAP)
	"*I would fall easily, I couldn't run or jump, and I found it hard to climb stairs.*" (Adult; AoO ≤2 years)	"*My mum or sister would have to help me with washing myself in the shower. I could not take baths as I could not get up from the bathtub.*" (Adult; AoO >2 to ≤12 years)	"*Today I can no longer walk, I depend on help from others to sit, take me to the bathroom, assistance in bathing, taking off and putting on clothes and shoes, I use non-invasive mechanical ventilation for exercises and sleep with it.*" (Adult; AoO ≤2 years)
Impacts on mental health	• Feeling different and socially isolated • One child experienced teasing • Sadness and frustration about not being able to complete tasks	• Fear of going out alone • Anxiety over mobility and embarrassment over falls and being different • Difficulty continuing studies or work outside the home	• Shame and fear due to falling and mobility issues • Frustration, fear and concern over declining abilities • Identity issues and distress related to full reliance on support • Insecurities and panic attacks related to use of breathing equipment
	"*In kindergarten, between the ages of ***, I became aware that my body was different from others. I walked slower and couldn't run or jump like the other kids.*" (Adult; AoO ≤2 years)	"*At first, it was difficult because I felt embarrassed to feel and look different, and I also felt a bit of guilt because I felt like I was giving up. But that same year, I travelled to Europe, and without the wheelchair, it would have been impossible for me to do so. I felt grateful for it because it meant being able to travel and see many places in the world without feeling tired.*" (Adult; AoO ≤2 years)	"*The fatigue, difficulty walking short distances, climbing, difficulty getting up from a chair, climbing stairs. This brings you a lot of insecurity and even shame.*" (Adult; AoO ≤2 years)

AoO, age of TK2d symptom onset; BiPAP, bilevel positive airway pressure; TK2d, thymidine kinase 2 deficiency.

- As symptoms worsened and additional symptoms emerged during adolescence and adulthood, the impacts on daily life and need for support and adaptations to assist with daily activities increased (**Figure 3**)
- The growing reliance on others, loss of independence and declining ability to participate in social activities and/or to attend school/work contributed to an increasing mental health burden

Factors contributing to a 'challenging' day

- Factors leading to a 'challenging' day, spontaneously reported by participants, included a meaningful worsening in generalized fatigue (7/9), respiratory and swallowing difficulties (5/9; which in some cases presented together), and muscular/neurological symptoms (4/9)
- Improvement or worsening of symptoms primarily affected three HRQoL domains: mobility, daily activities and independence

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