Assessment of the thymidine kinase 2 deficiency (TK2d) diagnostic and care pathways—rationale for a modified Delphi survey consensus panel

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Introduction

- Thymidine kinase 2 deficiency (TK2d) is an ultra-rare, autosomal-recessive mitochondrial DNA maintenance disorder caused by \(TK2\) gene mutations that leads to progressive muscle weakness, need for ventilatory support, and premature death in most patients\(^1,2\).

- Previous research has demonstrated that diagnosing mitochondrial disease can be difficult and burdensome due to its rarity, physicians’ lack of awareness of mitochondrial disease, and the heterogeneity of symptoms\(^3\).

- In fact, patients with mitochondrial disease may consult 8 physicians on average prior to their diagnosis\(^3\).

- The lack of consensus guidelines on TK2d diagnosis and treatment may result in confusion and variability in TK2d management.

References

Rationale for a Modified Delphi Survey

• A recent 60-minute telephone survey of 11 international physicians was conducted to document current management of TK2d
  – Interviewed physicians included neurologists, neuromuscular specialists, and geneticists who cared for patients with TK2d (median age: 3 years; range: 2-8 years)

• Results from the survey indicate that:
  – Patients were referred by a primary physician to a neurologist or a neuromuscular specialist and less often to a geneticist (Figure 1)
  – Misdiagnosis was common due to lack of disease awareness
  – A lead physician working with a multidisciplinary team coordinated ongoing management of patients
  – Clinicians’ overall aim for patients was to maintain quality of life; additional goals varied by age of onset
  – Supportive care for manifestations of TK2d and social support were high priorities

• Conducting a modified Delphi survey may help achieve consensus on diagnosing and treating patients with TK2d and may narrow gaps in TK2d diagnosis and management
  – The Delphi process has been used to develop consensus statements on mitochondrial disease management1-3

Figure 1. TK2d care pathway

References
Methodology for the Proposed Modified Delphi Survey

- The Delphi process is a practical and structured method used to achieve consensus on a particular topic from many individuals.\(^1,2\)

- For this survey, we propose that participants rate a set of carefully selected statements derived from a synthesis of the literature in a structured and transparent process (Figure 2).\(^1,3-6\)
  - Clinicians with experience in managing TK2d anonymously provide responses to statements in multiple rounds of sequential questionnaires
  - After each round, a summary of the participants’ responses is provided and is used to modify statements in the next round
  - The process ends when consensus is reached

- Suggested statements are shown in Table 1

**Figure 2. Proposed modified Delphi survey process**

**References**


TK2d, thymidine kinase 2 deficiency.
Examples of Proposed Statements for Review

- Participants will express their level of agreement or disagreement with each statement (Table 1) using a 5-point Likert scale (1=strongly disagree; 2=disagree; 3=neither agree nor disagree; 4=agree; 5=strongly agree).

Table 1. Proposed statements for review, by category

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<th>Category</th>
<th>Proposed Statement</th>
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| Clinical presentation           | Age of onset often predicts the severity and rate of progression of TK2d, with later age of onset associated with a slower rate of progression.¹  
Dysphagia, ptosis, and mtDNA multiple deletions may separate individuals with late-onset vs early-onset TK2d.²  
The diagnosis of TK2d can be established in individuals with bi-allelic pathogenic variants in TK2 identified by molecular testing AND/OR:  
  - Severely reduced (typically <20% of age- and tissue-matched healthy controls) mtDNA content in skeletal muscle by muscle biopsy in infants aged ≤2 years  
  - Reduced mtDNA content or multiple mtDNA deletions, ragged red fibers, and/or COX-deficient fibers in skeletal muscle biopsy in individuals age >2 years  
It may be useful to consider age at onset before determining the best test to reach a diagnosis. In patients with early-onset disease with cardinal symptoms of muscle weakness and respiratory difficulties, a small mitochondrial myopathy or an mtDNA panel should be considered. The results of muscle biopsy and/or additional genetic testing can be used to direct subsequent genetic studies.³⁴  
However, with advances in next-generation sequencing technology, comprehensive diagnosis using target panels or whole exome sequencing may be used before muscle biopsy, which can be painful and invasive.³  
To establish disease severity and needs of individuals with diagnosed TK2d, recommended evaluations include an assessment of chewing and swallowing ability, hearing, and pulmonary function; a neurologic examination; an EEG; and a motor/developmental assessment. Consultation with a clinical geneticist or a genetic counselor is also recommended.³  
Serum GDF-15 level is under research as a potentially sensitive and specific biomarker for monitoring the severity and progression of mitochondrial myopathies, including TK2d, and their response to treatment.⁵  
Surveillance for individuals with TK2d should include an assessment of nutritional status, weight gain, and growth, pulmonary function, and blood gases; an audiology evaluation; and neurodevelopmental assessments.³  |

References

Conclusions
• Evidence suggests the need for increased understanding of TK2d
• Development of a modified Delphi survey to achieve consensus on diagnostic work-up and treatment strategies may reduce variability in management of patients with this disease
• Accurate and timely diagnosis can lead to the initiation of effective treatment that could prevent disease progression and significantly improve quality of life

TK2d, thymidine kinase 2 deficiency.