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Pearls and Oy-sters: Case Report of a Patient With Adult-Onset Thymidine Kinase Gene (TK2) Deficiency

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Pearls

- Mitochondrial disorders (such as thymidine kinase 2 gene (*TK2*) deficiency) should be considered in the differential diagnosis of patients with clinical and electrodiagnostic evidence of neuropathy and myopathy.
- Clinical recognition of this disorder is important for adequate management and potential enrollment in clinical trials for *TK2* nucleoside replacement therapy.

Oy-sters

- High clinical suspicion of *TK2* deficiency is needed due to heterogeneous presentations with a wide spectrum of clinical manifestations.
- Acute worsening of symptoms, including rhabdomyolysis, can be seen in mitochondrial disorders and may mimic autoimmune neuromuscular conditions.

Case Report

We report the case of a 40-year-old man with no past medical history who presents with acute on chronic muscle weakness and respiratory failure. Throughout his childhood, he was of small stature but able to keep up with his peers. At the age of 21, he developed limb girdle weakness. He lost the ability to stand up from a squat and had trouble lifting his children once they were above 30 pounds. A year later, he developed bilateral ptosis and underwent blepharoplasty. He was lost to follow up until the age of 39, when he was evaluated for tonsillitis, and was found to have ongoing ptosis,

hypernasality of speech, and dysphagia. A CT of the neck showed diffuse muscular atrophy. He was referred to a neuromuscular specialist for further work up but was again lost to follow up.

At the age of 40, he presented with two days of worsening weakness, progressive orthopnea, dysarthria, and dysphonia. He was no longer able to climb stairs or lift his arms above his head. He was not taking any medications. Initial neurologic examination revealed ptosis, hypophonia, nasal speech, pooled secretions, decreased single breath count (6 breaths per minute, normal 12-16), ophthalmoparesis, facial diplegia, decreased muscle bulk throughout, neck flexion weakness (Medical Research Council (MRC) 2/5) and proximal greater than distal arm and legs weakness (MRC 4/5 bilaterally) with normal sensation to vibration and pinprick and intact reflexes. Serum studies showed elevated muscle enzymes and inflammatory markers (initial CK 9702 which decreased by around 2000 per day until normalization, range of normal: 49 - 397 U/L), aldolase 96, AST 382, ALT 224, ESR 87, creatinine 0.26) and hypercarbic respiratory failure (VBG 7.38/66, negative inspiratory force -10, forced vital capacity 0.75 L). Serum lactate was normal. Due to concern for concurrent myasthenia gravis exacerbation or an inflammatory myopathy, he was treated with 5 days of IVIG (total 2 g/kg) with minimal improvement. His myasthenia gravis antibodies, including acetylcholine binding and blocking antibodies as well as anti-MUSK antibody were negative. Immune mediated necrotizing myopathy was also on the differential, but his anti-3-hydroxy-3-methylglutaryl coenzyme A reductase (anti-HMGCR) and anti-signal recognition particle (anti-SRP) were negative. His myositis panel also came back negative, which made dermatomyositis and anti-synthetase inflammatory myopathy also less likely (negative antibodies for Anti-Jo1, Anti-PL7, Anti-PL12, Anti-OJ, Anti-EJ, Anti-RNP, Anti-SSA, Anti-Ku, Anti-PM-Scl-100, Anti-fibrillarin, Anti-Mi-2, Anti-P155/140, Anti-TIF-1 gamma, Anti-SAE, Anti-MDA5, Anti-NXP-2). The remaining serum studies showed no evidence of inflammatory, autoimmune, or infectious conditions (ANA negative, ganglioside antibodies revealed elevated GD1a and GM2 of unclear significance, acute hepatitis negative, COVID/Flu negative). Echocardiogram was normal. MRI brain (T1) showed bright tongue sign (Figure). Nerve conduction studies (NCS) showed a length-dependent axonal sensory-motor neuropathy and needle

electromyography (EMG) showed generalized myopathy and muscle membrane irritability. The combination of neuropathy and myopathy, along with ptosis and extraocular movement impairment raised concern for a mitochondrial disorder, and made myasthenia gravis or an immune mediated myopathy less likely. He underwent rapid exome sequencing, mitochondrial DNA sequencing and deletion/duplication studies which revealed a homozygous pathogenic variant in the *TK2* gene (c.604_606del [p.K202del]). His mother was found to be a heterozygous carrier of the pathologic variant and his father is presumed to be a carrier.

During his admission, he developed worsening respiratory failure, requiring intubation. He was eventually transitioned to AVAPS at night with cough assist. A jejunostomy for feeding was performed secondary to severe oropharyngeal dysphagia. He was discharged home with close follow up at neuromuscular multi-disciplinary clinics for mitochondrial supplement cocktail, pulmonary and cardiac monitoring, and to determine if he is eligible for a *TK2*-specific clinical trial (MT1621) or other clinical trials for mitochondria myopathies.

Discussion:

The mitochondrial DNA (mtDNA) depletion syndromes are autosomal recessive disorders characterized by decreased mtDNA copy number in affected tissues. Mutations in the *TK2* gene has been identified in patients with the myopathic form of this syndrome. *TK2* is a nuclear gene that encodes a mitochondria-specific enzyme in the pyrimidine salvage pathway. The enzyme is needed for the phosphorylation of pyrimidine nucleosides and pathogenic variants cause reduction of mtDNA content, reducing the ability for mitochondria to create the energy needed for cells to function properly.¹⁻⁷

TK2 deficiency causes a spectrum of clinical severity with a wide range of age of onset.^{1,3-6} It was first described in 2001 in four children with severe myopathy; but it was not until 2012 when the first two cases of adult-onset form were identified, both occurring in the fifth decade of life, characterized by chronic progressive external ophthalmoplegia (CPEO), limb girdle weakness and dysphagia.^{2,3,5,6} Three clinical forms have been proposed: infantile onset (<1 year old, 40% of cases), childhood onset (1-18

years old, 41% of cases), and adult onset (>18-year-old, 19% of cases).^{1,3} It has been postulated that the range of phenotypes observed may be explained by the variability in the amount of functioning activity of the mutated enzyme in specific tissues.^{1,6} Due to unknown prevalence with only around 107 cases with over 30 distinct pathogenic variants identified as of 2018, classification of genotype-phenotype correlations is currently limited, though some associations between variant and clinical manifestations have been observed.^{1,6}

The adult-onset form is the least common and less severe than other forms. It is characterized by proximal muscle weakness, dysphagia, and respiratory insufficiency.¹⁻⁶ Percutaneous gastrostomy tubes were required in around 30% of patients.³ Supportive findings include elevated CK usually 5-10 times the upper limit of normal and severely reduced MtDNA content from either depletion or deletions.¹

Patients with *TK2* mutations often have delayed diagnosis, taking on average 17.4 years from disease onset to diagnosis.¹⁻⁷ There are several features of this case that made initial diagnosis in our patient more challenging. First, while he had prior history of proximal weakness, respiratory muscle atrophy, and ptosis, on re-presentation, he had rapid decline over two days in his proximal weakness and respiratory function without evidence of a mitochondrial trigger (i.e. infection, fasting, hypovolemia, surgical procedure). This rapid decline is atypical in mitochondrial disorders which usually follow a more indolent course, though acute presentations have been described.⁷ Second, his creatine kinase (CK) was forty times the upper limit of normal, whereas mitochondrial myopathies have a CK that is typically normal or mildly elevated to less than ten times the upper limit of normal.^{1,3} Of the patients identified with *TK2* late-onset myopathy, the highest CK that has been noted was 2453 whereas our patient's CK was 9702.³ The rapid decline in his proximal and respiratory weakness and his elevated CK made an inflammatory myopathy possible, prompting treatment with IVIG. Medications such as valproic acid and aminoglycosides should be avoided as they can disrupt mtDNA replication and translation or have downstream effects on the respiratory chain depending on the mutation.⁸ Lastly, with only around 18 patients identified as of 2018, the natural history of the disease has not been fully characterized.³ Other mtDNA transcriptome defects, such as *DGUOK*, *DNA2*, *MGME1*,

POLG, *POLG2*, and *TWNK* also present in adulthood and cause skeletal muscle dysfunction, ptosis and ophthalmoplegia, in addition to the single large scale mtDNA deletion syndromes (SLSMDS) such as Kearns Sayre syndrome. Genetic testing, including mtDNA sequencing and deletion studies, is essential to differentiate mitochondrial disorders. Late onset spinal muscular atrophy, congenital myopathies, Pompe disease, and certain muscular dystrophies also should remain on the differential.¹⁻⁶ In addition, he had bright tongue sign on his Brain MRI, which is commonly seen in Pompe disease (Figure).⁹

There are some key distinguishing features of this case that should have made a mitochondrial disorder higher on the differential despite the red herrings above. First, his history of ptosis and CPEO is a sign of a mitochondrial disorder and can be seen as an isolating feature of *TK2* myopathy.^{1,3,10} Second, his EMG/NCS showed not only a generalized myopathy but also a length-dependent axonal sensory-motor neuropathy (Table), which is present in around 40% of patients with adult-onset form.³ The combination of CPEO and pattern of both myopathy and neuropathy seen on his electrodiagnostic study solidified the concern for a mitochondrial disorder, prompting genetic testing.

Clinical trials for nucleoside substrate enhancement therapy designed specifically for *TK2* deficiency are ongoing, making early diagnosis more imperative. The drug, MT1621, consists of a combination of deoxynucleosides which has in preclinical mouse models shown to increase mtDNA copy number and improve cell function and overall lifespan.^{3,11} Expanded access programs are available, allowing patients for the first time have the potential to benefit from a targeted nucleoside replacement therapy.¹² Gene therapy replacement is also being investigated in pre-clinical trials with promising results.¹³ There are also a growing number of clinical trials for adults with primary mitochondrial myopathy.

This case highlights that *TK2* deficiency should be considered in patients with CPEO, proximal weakness, and respiratory insufficiency, even in the presence of acute on chronic decline and elevated CK values above ten times the upper limit of normal. The prognosis of this disorder is often poor due to the high risk of progressive

respiratory insufficiency. Diagnosis is now crucial so that patients can be enrolled to receive the potential benefit of *TK2* replacement therapy.

Table: NCS (November 2022)

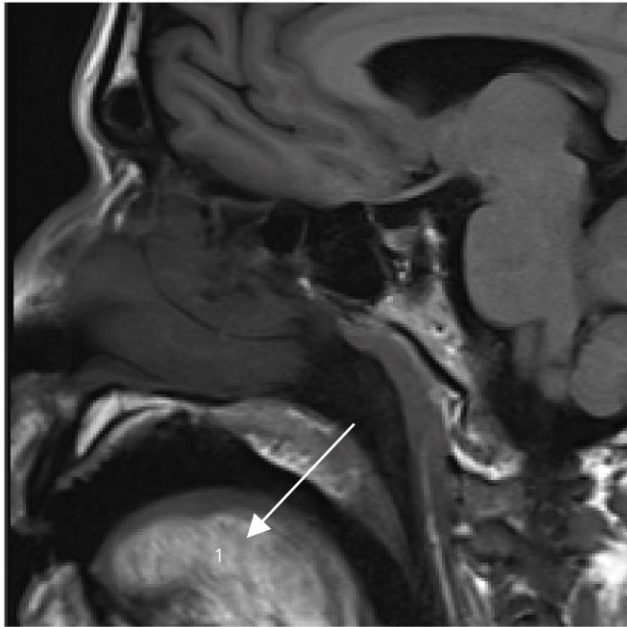
<u>Sensory Nerve Conduction Studies</u>					
Nerve/Sites	Lat1 ms	Lat2 ms	Dist mm	CV m/s	Amp uV
Left Median- Rec Index (Antidromic)					
Wrist	NR	NR			NR
Left Ulnar – Rec Digit V (Antidromic)					
Wrist	NR	NR			NR
Left Radial – Rec Anatomic snuff box (Antidromic)					
Wrist	1.9	2.3	95	51	17
Left Sural – Rec Ankle					
Lower Leg	NR	NR			NR
<u>Motor Nerve Conduction Studies</u>					
Nerve/Sites	Lat ms	Dist mm	Dur ms	CV m/s	Amp mV
Left Median- Rec APB, C8-T1					
Wrist	3.5	70	7.1		3.8
Elbow	7.7	220	8.4	52	3.8
Exercise	3.5		7.0		3.7
Left Ulnar – Rec ADM, C8-T1					
Wrist	3.1	70	5.5		5.1
Below elbow	7.0	240	5.8	63	4.4
Exercise	3.1		5.6		5.2

Left Peroneal (Fibular) – Rec EDB, S1-S2					
Ankle	3.6	90	7.0		0.4
Fibula (head)	8.8	320	8.1	61	0.6
Popliteal fossa	10.3	85	6.9	57	0.5
Left Peroneal (Fibular)- Rec TA, L4-L5					
Fibula (head)	1.7		9.0		2.6
Popliteal Fossa	3.2	85	8.6	57	2.5
Left Tibial – Rec AH, S1-S3					
Ankle	NR		NR		NR

Key: Lat: Latency, ms: milliseconds, Dist: distance, mm: millimeter, CV: conduction velocity, m/s: meter per second, amp: amplitude, μ V: micro volts*, mV: milli volts, NR: non-reactive, Dur: duration, APB: Abductor pollicis brevis, ADM: Abductor digiti minimi, EDB: extensor digitorum brevis, TA: Tibialis Anterior, AH: abductor hallucis

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Figure: MRI Brain (11/2022): There is a bright tongue sign (1) on the sagittal view of his T1 MRI brain. The T1 hyperintensity reflects fatty infiltration of the tongue muscle. This is seen in neuromuscular conditions that affect bulbar muscles, which is often missed by radiologists. His MRI brain was otherwise unremarkable.⁹



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