Clinical Reasoning:

A 58-year-old man with progressive ptosis and walking difficulty

Pei-Hsin Kuo, MD
Raymond Y. Lo, MD,
PhD
Kurenai Tanji, MD, PhD
Sheng-Han Kuo, MD

Correspondence to
Dr. Kuo:
sk3295@columbia.edu

SECTION 1

A 58-year-old man developed progressive walking difficulty over 10 years. He had normal development and an unremarkable birth history. At age 30, he developed bilateral drooping eyelids with double vision. At age 48, he developed progressive gait unsteadiness, slurred speech, and swallowing difficulty. At age 55, he needed to walk with a cane. He did not have seizures, hearing loss, or memory impairment. He did not have any history of alcohol abuse or exposures to anticonvulsants. His mother has congenital cardiac disease and diabetes mellitus, and his sister has had epilepsy since childhood. His daughter is healthy.

On examination, the patient had left exotropia and bilateral ptosis without fatigability. His pupillary reflex to light was normal. He had partial horizontal gaze palsy and lack of upward gaze, which was not

overcome by vestibulo-ocular reflex. His saccadic eye movements were slow without nystagmus or square wave jerks. He had scanning speech. He had normal muscle power but decreased vibratory sensation and proprioception in his legs, and his deep tendon reflexes were absent. He had mild bradykinesia and arm rigidity without rest tremor. He had mild dysmetria in bilateral finger-nose-finger, finger chase, and heel-shin slide examinations and he had impaired rapid alternating movements. He had wide-base gait with variable stride length but good heel strike, and he could not perform tandem gait (video at Neurology.org).

Questions for consideration:

1. What is the phenomenology?
2. What are the differential diagnoses?

[GO TO SECTION 2](#)

Supplemental data
at Neurology.org

From the Departments of Neurology (P.-H.K., K.T., S.-H.K.) and Pathology and Cell Biology (K.T.), Columbia University, New York, NY; and the Department of Neurology (P.-H.K., R.Y.L.), Buddhist Tzu Chi General Hospital, Hualien, Taiwan.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

SECTION 2

This patient had parkinsonism, including bradykinesia and rigidity. Dysmetria, dysdiadochokinesia, variable stride length, and impaired tandem gait suggested cerebellar ataxia.

Multiple system atrophy (MSA) should be considered in a patient older than 50 years with parkinsonism and ataxia; however, we did not detect any autonomic dysfunction or pyramidal sign. Although ophthalmoplegia could be suggestive of progressive supranuclear palsy (PSP), the patient's impaired vertical gaze is not of supranuclear type, because his gaze palsy could not be overcome by the vestibulo-ocular reflex.¹ Besides, his ptosis, horizontal gaze palsy, and sensory neuropathy were not consistent with MSA or PSP. Although rare in patients older than 50 years, spinocerebellar ataxias (SCAs) should still be in the differential diagnoses. SCAs may cause parkinsonism, ataxia, and sensory neuropathy, especially in SCA2 and SCA3. SCA2 is characterized by absent reflexes and slow saccades, whereas patients with SCA3 could have proptosis

and ophthalmoplegia. However, ptosis is not a common sign in SCAs.

Reversible causes of cerebellar ataxia should also be excluded. Immune-mediated cerebellar ataxia associated with anti-glutamic acid decarboxylase, anti-gliadin, anti-thyroglobulin, or paraneoplastic antibodies should be examined. Vitamin E, vitamin B₁, or vitamin B₁₂ deficiency should be on the list of differential diagnoses, for patients with Wernicke encephalopathy (WE) may also present with ataxia and ophthalmoplegia.

The patient's chronic progressive ptosis and ophthalmoplegia, which are characteristic for progressive external ophthalmoplegia (PEO), raised the possibility of mitochondrial disorder. PEO is a common feature in mitochondrial disorders, and patients with PEO rarely complain of diplopia because of its slowly progressive nature, such as in our case.

Questions for consideration:

1. What tests should we order?
2. What is the next step?

GO TO SECTION 3

(A) Succinate dehydrogenase (SDH) stain (100×) shows muscle fibers with increased staining, indicating mitochondrial proliferation (arrows). (B) Combined SDH (blue) and cytochrome c oxidase (COX) (brown) stain (100×) show COX-negative fibers with strong SDH stain, demonstrating muscle fibers with respiratory chain defects with corresponding mitochondrial proliferation (arrows).

SECTION 3

All immunologic markers, including paraneoplastic antibodies, were normal in this patient. Vitamin E and vitamin B₁₂ levels were also normal. His brain MRI was unremarkable, and it did not show typical signs of WE, such as T2 hyperintensity lesions over mammillary bodies, dorsomedial thalami, tectal plate, or periaqueductal area.² His dopamine transporters scan revealed decreased uptake in bilateral striatum and his bradykinesia and rigidity responded to levodopa, suggesting levodopa-responsive parkinsonism.

The patient's creatine phosphokinase levels were high (526 U/L) with a normal venous lactate level. His nerve conduction study showed axonal polyneuropathy with absent sensory nerve action potentials in all limbs.

Muscle biopsy at the patient's right biceps showed mitochondrial cytopathy with increased succinate dehydrogenase (SDH) staining. Approximately 30% of muscle fibers showed various degrees of cytochrome c oxidase (COX) deficiency by an SDH-COX double stain (figure).

Questions for consideration:

1. How do you interpret the muscle pathology findings?
2. What would you do next to differentiate among mitochondrial diseases?

GO TO SECTION 4

SECTION 4

SDH staining is a sensitive and specific marker for mitochondrial distributions in muscle fibers, and increased SDH staining in the patient's muscle fiber indicates mitochondrial proliferation, which may be a compensatory response to mitochondrial dysfunction. Another traditional way to assess mitochondrial proliferation is Gomori trichrome stain, which shows classic ragged-red fibers. COX is complex IV of the respiratory chain, and COX deficiency reflects respiratory chain dysfunction. The combined COX-SDH stain showed increased COX-negative fibers with strong SDH stain, indicating impaired respiratory chain with compensatory mitochondrial proliferation, and it is a typical finding in disorders of mitochondrial DNA (mtDNA) deletions.

Further analyses of muscle tissues showed decreased activities of mitochondrial respiratory chain enzyme complex I, I + III, II + III, and IV. Multiple defects in the complexes imply a wide-ranged dysfunction of the respiratory chain, as each complex is composed of subunits encoded by both mtDNA and nuclear DNA (nDNA), except for complex II, which only constitutes proteins encoded by nDNA.

The extensive defects in the respiratory chain complex might result from single large deletion of mtDNA, t-RNA mutation in the mtDNA, or nDNA defect leading to secondary mtDNA abnormality. We performed Southern blot analysis to investigate mtDNA integrity, which revealed multiple mtDNA deletions. Using quantitative PCR with probes for both mtDNA and nDNA, we discovered that the amount of mtDNA was partially depleted (37%). Marked mtDNA depletion usually occurs in severe early-onset disease, while multiple mtDNA deletions without depletion often result in late-onset diseases or milder neurologic symptoms. The latter is usually caused by the defects of machinery to maintain mtDNA, including polymerase γ mutation.³ Polymerase γ is a nuclear-encoded mitochondrial protein that is responsible for mtDNA replication, and *POLG* mutation can lead to partial mtDNA depletion and cause a clinical syndrome of sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO). Therefore, we performed targeted sequencing of *POLG* gene and identified a heterozygous missense mutation 2864A>G (Y955C), which is known to cause PEO and ataxia.

DISCUSSION Our patient has cerebellar ataxia, levodopa-responsive parkinsonism, sensory neuropathy, and PEO, associated with *POLG* mutation. Human mtDNA is replicated by DNA polymerase γ , which is critical for mtDNA

integrity, and the catalytic subunit with high fidelity is encoded by *POLG*.³ A number of mutations have been identified across the entire *POLG* gene, and missense mutations, such as in our case, account for more than 90% of *POLG*-related neurologic disorders. Mutations in *POLG* compromise function of DNA polymerase γ and it results in secondary mtDNA defects, including depletion, deletions, and base pair substitution.³ Secondary mtDNA mutation gives rise to defective oxidative phosphorylation and ATP production in mitochondrial respiratory chain.⁴ With longer disease duration, mtDNA deletions and mutations accumulate, and eventually lead to neuronal death in selectively vulnerable regions in mitochondrial dysfunction such as basal ganglia and cerebellum.⁵ In *POLG*, Y955 specifically plays a critical role in catalysis and fidelity of DNA synthesis,⁶ and it is highly conserved in different species.^{4,6}

POLG mutations can lead to wide-variable clinical presentations. The age at disease onset varied from 3 months to 66 years.⁷ The most severe form of *POLG* mutations is Alpers syndrome, with clinical features of early-onset psychomotor regression, intractable epilepsy, and liver failure. SANDO syndrome is another common presentation with sensory ataxic neuropathy, dysarthria, and ophthalmoparesis. *POLG* mutation is also known to be associated with myopathy and dementia, cardiac arrhythmia, cardiomyopathy, diabetes, and ovarian failure.³ PEO is the most common sign in patients with Y955C, although levodopa-responsive parkinsonism has also been reported, as in our case.⁸

Multifocal T2 hyperintensities and brain atrophy in head MRI can be found in some but not all patients with *POLG* mutation.³ Likewise, lactatemia is a supportive but not a diagnostic feature in patients with *POLG* mutation.⁹ Muscle histochemical studies might be normal findings, or show ragged-red fibers or isolated scattered COX-deficient fibers, depending upon the state of respiratory chain function. Respiratory chain enzyme assay might also reveal decreased activity in single or multiple complexes, or even normal activity. Therefore, the lack of laboratory or histologic mitochondrial dysfunction evidence does not exclude *POLG*-related disorders.³

There are many phenotypic variants among *POLG*-related disorders, even with the same mutation and within the same family. The recognition of the wide-ranged clinical spectrum of *POLG* mutations is important for proper diagnosis. Currently, there is no effective treatment for *POLG*-related disorders.³ Novel treatments for diseases of mtDNA deletions, such as thymidine kinase mutations, have been developed,¹⁰ shedding light on mechanism-based therapy for mitochondrial disorders.

AUTHOR CONTRIBUTIONS

Pei-Hsin Kuo: literature search, drafting the manuscript. Raymond Y. Lo: literature search, critical revision of the manuscript. Kurenai Tanji: literature search, critical revision of the manuscript. Sheng-Han Kuo: primary patient care, literature search, critical revision of the manuscript.

STUDY FUNDING

Dr. Kuo has received funding from NINDS K08 NS08738 (principal investigator), Louis V. Gerstner Jr. Scholar Award, Parkinson's Disease Foundation, American Academy of Neurology Research Fellowship, American Parkinson's Disease Association, International Essential Tremor Foundation, NIEHS pilot award ES009089, and the Smart Foundation.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES

1. Lopez G, Bayulkem K, Hallett M. Progressive supranuclear palsy (PSP): Richardson syndrome and other PSP variants. *Acta Neurol Scand* 2016;134:242–249.
2. Kuo SH, Debnam JM, Fuller GN, de Groot J. Wernicke's encephalopathy: an underrecognized and reversible cause of confusional state in cancer patients. *Oncology* 2009;76:10–18.
3. Milone M, Benarroch EE, Wong LJ. POLG-related disorders: defects of the nuclear and mitochondrial genome interaction. *Neurology* 2011;77:1847–1852.
4. Van Goethem G, Dermaut B, Lofgren A, Martin JJ, Van Broeckhoven C. Mutation of POLG is associated with progressive external ophthalmoplegia characterized by mtDNA deletions. *Nat Genet* 2001;28:211–212.
5. Tzoulis C, Tran GT, Coxhead J, et al. Molecular pathogenesis of polymerase gamma-related neurodegeneration. *Ann Neurol* 2014;76:66–81.
6. Graziewicz MA, Bienstock RJ, Copeland WC. The DNA polymerase gamma Y955C disease variant associated with PEO and parkinsonism mediates the incorporation and translesion synthesis opposite 7,8-dihydro-8-oxo-2'-deoxyguanosine. *Hum Mol Genet* 2007;16:2729–2739.
7. Cohen BH, Naviaux RK. The clinical diagnosis of POLG disease and other mitochondrial DNA depletion disorders. *Methods* 2010;51:364–373.
8. Luoma P, Melberg A, Rinne JO, et al. Parkinsonism, premature menopause, and mitochondrial DNA polymerase gamma mutations: clinical and molecular genetic study. *Lancet* 2004;364:875–882.
9. Tchikviladze M, Gilleron M, Maisonnobe T, et al. A diagnostic flow chart for POLG-related diseases based on signs sensitivity and specificity. *J Neurol Neurosurg Psychiatry* 2015;86:646–654.
10. Garone C, Garcia-Diaz B, Emmanuele V, et al. Deoxypyrimidine monophosphate bypass therapy for thymidine kinase 2 deficiency. *EMBO Mol Med* 2014;6:1016–1027.

Neurology®

Clinical Reasoning: A 58-year-old man with progressive ptosis and walking difficulty

Pei-Hsin Kuo, Raymond Y. Lo, Kurenai Tanji, et al.

Neurology 2017;89:e1-e5

DOI 10.1212/WNL.0000000000004064

This information is current as of July 3, 2017

Updated Information & Services	including high resolution figures, can be found at: http://n.neurology.org/content/89/1/e1.full
Supplementary Material	Supplementary material can be found at: http://n.neurology.org/content/suppl/2017/07/03/WNL.0000000000004064.DC1
References	This article cites 10 articles, 3 of which you can access for free at: http://n.neurology.org/content/89/1/e1.full#ref-list-1
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Diplopia (double vision) http://n.neurology.org/cgi/collection/diplopia_double_vision Eyelids http://n.neurology.org/cgi/collection/eyelids Gait disorders/ataxia http://n.neurology.org/cgi/collection/gait_disorders_ataxia Mitochondrial disorders http://n.neurology.org/cgi/collection/mitochondrial_disorders Parkinson's disease/Parkinsonism http://n.neurology.org/cgi/collection/parkinsons_disease_parkinsonism
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.neurology.org/about/about_the_journal#permissions
Reprints	Information about ordering reprints can be found online: http://n.neurology.org/subscribers/advertise

Neurology® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2017 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.