Orthostatic tremor (OT) is a rare high-frequency (13-18 Hz) leg tremor occurring in standing position. It is thought to be sporadic but siblings with OT from 3 unrelated families were reported. No mutations have been reported in OT. We describe a patient with OT carrying a C10orf2 TWINKLE mutation to highlight the possible association of OT with mitochondrial dysfunction and mutations in the mitochondrial replicative helicase Twinkle.

**Report of a Case**

The mitochondrial study received institutional review board approval, and the patient provided informed consent to participate in the study. A man in his late 60s had ptosis and tremor on standing for 30 years, followed by development of progressive external ophthalmoplegia. Polygraphic recordings revealed an orthostatic synchronous tremor with 17.5-Hz frequency. Electromyography/nerve conduction studies showed evidence for a mild myopathy and associated mild axonal sensorimotor peripheral neuropathy. Muscle biopsy revealed ragged red fibers; mild cerebral atrophy was evident by magnetic resonance imaging. Molecular analysis revealed a novel heterozygous missense mutation at an evolutionarily conserved residue of the C10orf2 TWINKLE gene.

We describe herein a patient with OT occurring in association with progressive external ophthalmoplegia and a heterozygous mutation in the gene encoding for the mitochondrial DNA (mtDNA) helicase Twinkle (C10orf2 TWINKLE), raising the possibility that loss of mitochondrial DNA integrity may play a role in the pathogenesis of OT.

**Conclusions and Relevance**

Although the incidental association of OT and C10orf2 TWINKLE mutation is possible, the simultaneous onset of OT and eyelid ptosis at a much younger age than usually observed for OT raises the possibility of mitochondrial dysfunction and loss of mitochondrial DNA integrity in the pathogenesis of OT.
Paresis, reduced Achilles reflexes, and bilateral leg tremor only on standing. He had no clinical evidence for parkinsonism or cerebellar dysfunction. The only medications he was taking were hydralazine, carvedilol, and candesartan cilexetil for hypertension; ezetimibe for hypercholesterolemia; and levothyroxine sodium for hypothyroidism. His family history was reportedly significant for bilateral eyelid ptosis and limited eye movements in an older sister and ptosis in a son in his early 40s. The patient's creatine kinase and blood lactate values were within normal limits. Thyrotropin, liver enzymes, ferritin, blood manganese and mercury, and serum copper and ceruloplasmin levels were also normal. One to 2 ragged red fibers per fascicle were present in many fascicles in the muscle biopsy specimen. Electromyography/nerve conduction studies showed evidence for a mild myopathy and mild axonal sensorimotor peripheral neuropathy. Polygraphic recordings revealed an orthostatic synchronic tremor with 17.5-Hz frequency primarily involving the legs (Figure 1). When he leaned forward supporting his arms on the back of a chair, the lower extremity tremor attenuates and a prominent upper extremity tremor of similarly high frequency emerges. B, The power spectra analyses confirm a frequency peak at around 17.5 Hz in all muscles.

Southern blot analysis of muscle mtDNA showed multiple mtDNA deletions. Sequencing of all coding exons and flanking introns of C10orf2 TWINKLE, POLG, POLG2, and ANT1 detected a novel heterozygous missense variant, c.1364T>C (p.M455T), in the patient, the affected sister and son, and an asymptomatic son in his late 30s. No mutations were detected in POLG, POLG2, and ANT1, also linked to chronic progressive external ophthalmoplegia. Several factors support the pathogenicity of p.M455T in C10orf2 TWINKLE: methionine at codon 455 of Twinkle is evolutionarily conserved in vertebrate except for rat where there is alanine; 2 computer-based algorithms, SIFT and PolyPhen 2, predict p.M455T to be deleterious; and the mutation segregates with the ptosis and ophthalmoparesis and was not detected in more than 200 healthy controls and more than 1000 subjects screened for possible mitochondrial diseases.

Discussion

We identified a C10orf2 TWINKLE mutation in a patient with OT and progressive external ophthalmoplegia. This observation raises the question of a possible role of mitochondrial dysfunction in the genesis of OT, a disorder well characterized electrophysiologically but of obscure etiology and pathogenesis. Although considered sporadic, the few observed familial cases have suggested the possibility of a genetic etiology, but to our knowledge, no molecular defects have been reported in OT. The detection of a C10orf2 TWINKLE mutation in our patient might shed light on the pathogenesis of this form of tremor. We cannot prove that OT is the result of the mutated Twinkle and therefore cannot exclude the incidental coexistence of 2 independent neurological disorders, OT on one side and Twinkle-related progressive external ophthalmoplegia on the other side. However, the simultaneous manifestation of OT...
and bilateral ptosis in the late 30s and the onset of the OT at an age younger than commonly observed may favor a common pathogenesis. The lack of lactate peaks on brain magnetic resonance spectroscopy did not help in establishing or excluding the existence of a mitochondrial encephalopathy in our patient. Indeed, normal brain magnetic resonance spectroscopy has been observed in subjects with mitochondrial encephalopathy, including subjects with disorders of the mtDNA replication.\textsuperscript{11} The patient’s sister and son, who reportedly have ptosis and ophthalmoparesis, also carry p.M455T in \textit{C10orf2 TWINKLE}, consistent with the autosomal dominant inheritance of the mutation. The 2 affected family members reportedly have no tremor but have not undergone a neurological examination. In addition, the reported lack of OT in the affected family members could reflect the phenotypic variability of the \textit{C10orf2 TWINKLE}-linked mitochondrial disorder, or it could signal a lower penetrance of OT compared with progressive external ophthalmoplegia, as previously observed for the parkinsonism in families with \textit{C10orf2 TWINKLE} mutations.\textsuperscript{12,13} Variable penetrance and younger age could account for the lack of symptoms in the other son with the mutation.

\textbf{REFERENCES}


\textbf{ARTICLE INFORMATION}

\textbf{Accepted for Publication:} May 14, 2013.
\textbf{Published Online:} September 23, 2013.

\textbf{Author Contributions:} Dr Milone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

\textbf{Study concept and design:} Milone, Wong.
\textbf{Acquisition of data:} Milone, Klassen, Haas, Wong.
\textbf{Analysis and interpretation of data:} All authors.
\textbf{Drafting of the manuscript:} Milone.
\textbf{Critical revision of the manuscript for important intellectual content:} All authors.
\textbf{Obtained funding:} Milone.
\textbf{Administrative, technical, and material support:} Milone, Klassen.
\textbf{Study supervision:} Milone.

\textbf{Conflict of Interest Disclosures:} None reported.

\textbf{Funding/Support:} This study was supported by the Mayo Clinic Center for Translational Science Activities through grant UL1 RR024150 from the National Institutes of Health National Center for Research Resources (Dr Milone).

\textbf{Role of the Sponsor:} The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

\textbf{Previous Presentation:} This paper was presented in poster format at the American Academy of Neurology meeting, March 21, 2013; San Diego, California.