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Twinkle mutation in an Italian family with external progressive ophthalmoplegia and parkinsonism: A case report and an update on the state of art

Lorenzo Kiferle*, Daniele Orsucci, Michelangelo Mancuso, Annalisa Lo Gerfo, Lucia Petrozzi, Gabriele Siciliano, Roberto Ceravolo, Ubaldo Bonuccelli

Section of Neurology, Department of Clinical and Pathological Medicine, University of Pisa, via Roma 67, 56126 Pisa, Italy

HIGHLIGHTS

- We here describe a family with two sisters and one son affected by a PEO1 mutation.
- The sisters had a clinical parkinsonism confirmed by FP-CIT SCAN.
- The characteristics of parkinsonisms are fully described in the paper.
- The paper provides a short review of the phenotypes of the parkinsonisms associated to PEO1 mutation described in the literature.

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ABSTRACT

The objective is to describe the clinical phenotype and genetic basis of a family with autosomal dominant progressive external ophthalmoplegia and parkinsonism with a Twinkle mutation. The proband, an 82 years old female, reported since childhood bilateral eyelid ptosis, ophthalmoplegia, sensorineural hypoacusis, mild depression since she was 45, with a positive familiar anamnesis of eyelid ptosis (father, two sisters and a son). She developed mild bilateral parkinsonism with a moderate clinical response to levodopa. The ^{123}I-FP-CIT SCAN evidenced a marked bilateral putaminal reduction and moderate caudate uptake reduction. Her 79 years old sister reported eyelid ptosis since she was 45 with ophthalmoplegia and developed a mild bilateral rest and postural tremor with moderate right arm plastic hypertonia when she was 76. The parkinsonism was confirmed with ^{123}I-FP-CIT SCAN. One of the two sons presented eyelid ptosis since he was 30 years old, with peripheral neuropathy with biopsy evidence of myopathy. We identified a G1750A mutation in the *c10orf2* gene in the three patients. Mitochondrial dysfunction has been implicated in the pathogenesis of sporadic, idiopathic Parkinson disease (PD). In some cases, mitochondrial DNA primary genetic abnormalities or more commonly secondary rearrangements due to polymerase gamma (*POLG*) gene mutation can directly cause parkinsonism. Parkinsonism has been reported as a rare symptom associated to Twinkle (*c10orf2*). Parkinsonism has to be investigated in patients with PEO with analysis of Twinkle mutation.

Progressive external ophthalmoplegia (PEO) can be caused by a disorder characterized by multiple mitochondrial DNA (mtDNA) deletions due to mutations in the *PEO1* gene, encoding the mtDNA helicase Twinkle. Clinically it is characterized by bilateral and symmetrical ptosis since the young adulthood without a clear diplopia. The patients are often unaware of their decreased motility until it becomes severe. Myopathy, exercise intolerance, cataracts, hypogonadism, ataxia and sensory axonal neuropathy are common in the course of the disease [1]. Fatigue, pain, and depression may be present as well in patients with PEO [2]. A late onset parkinsonism has been described in few cases of PEO due to Twinkle mutations.

We here describe our findings in a family with late onset parkinsonism and PEO, with mutation of G1750A in the exon 1 of *PEO1* gene.

The proband (subject II-2) (Fig. 1), an 82 years old female, presented childhood bilateral eyelid ptosis, ophthalmoplegia, mild depression and sensorineural hypoacusis since she was 45. She underwent corrective eyelid surgery twice (in 1995 and 2004). She presented severe apneas during night with minimum saturation of 84% and she complained a gait disorder with disequilibrium and frequent falls since 5 years before our clinical observation. She came to our attention for the development of a mild postural tremor

* Corresponding author. Fax: +39 050992443.
E-mail address: l.kiferle@virgilio.it (L. Kiferle).

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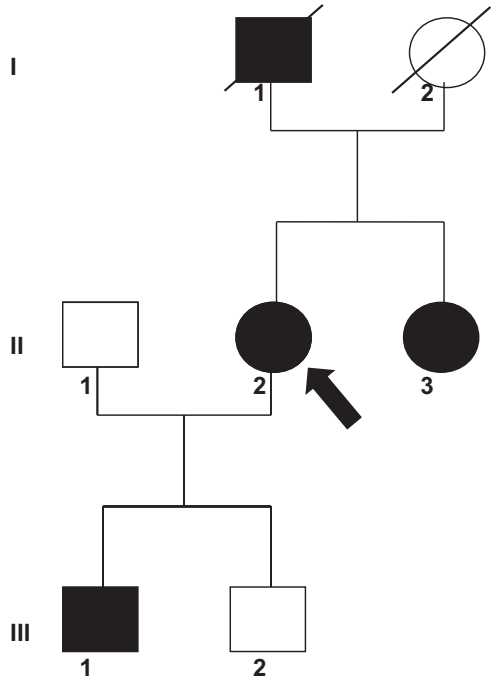

Fig. 1. Family tree. Squares and circles denote males and females, respectively. Black symbols indicate individuals with PEO. The arrow indicates the proband.

prevalent in left hand, mild bradykinesia and progressive smaller handwriting since one year and half. Clinical examination revealed bilateral ptosis and severe restriction of eye movements in all gaze directions with the evidence of previous surgical treatment and hypomimia, Mild hypokinesia, cogwheel mild rigidity of the left arm and mixed left predominant tremor (predominantly rest and postural tremor) and mild right leg rest tremor was also present at neurological examination. Gait was unsteady due to osteoarthrosis. A mild cognitive impairment was evident as well. Speech, muscle strength, tendon reflexes, plantar reflexes and sensation were normal. There was no muscle atrophy. Brain MRI was revealing a mild diffuse white matter chronic encephalopathy with a mild cortical–subcortical atrophy. She underwent ^{123}I FP-CIT SPECT (Fig. 2) with the evidence of a marked bilateral reduction of putaminal uptake and a mild reduction of caudate uptake. She was treated with 300 mg/day of levodopa with mild response to therapy.

Her 79 years old sister (subject II-3) was affected by eyelid ptosis since she was 45 years old and she performed a muscular biopsy when she was 64 years old, with the evidence of ragged red fibers, ragged blue fibers, 10% Cox-negative fibers. The ptosis was surgically corrected at the age of 56. She had an ischemic cardiac attack when she was 65 years old. She reported right hand tremor and bilateral small hands movement difficulties since she was 77. At clinical examination she presented bilateral ptosis, mild mandibular tremor, bilateral eyelid ptosis with incomplete ophthalmoplegia, mild bradykinesia and mild bilateral postural tremor (prevalent on the left side). A mild cogwheel rigidity on the left side was also present. A mild strength reduction was present at cingulus bilaterally and tendon reflexes were reduced. The ^{123}I FP-CIT SPECT revealed a bilateral putaminal reduction. She was not treated with levodopa as the signs were small and the parkinsonism remained stable for one year.

Their father was reported to have eyelid ptosis since the middle young age.

The 63 years old proband's son (III-1) had a bilateral ptosis since he was 30 years old (treated surgically in 2004) with chronic fatigue and occasional hand numbness. He underwent muscular biopsy in 1994 with the evidence of ragged red fibers, Cox-negative fibers, altered mitochondria at ultrastructural exam. At clinical examination he presented mild bilateral ptosis, horizontal diplopia in primary position, absent deep tendon reflexes, with ENG finding of axonal sensory polyneuropathy. His lactate levels were mildly increased after exercise. Gait was normal. No tremor or bradykinesia was evidenced. A mild rigidity was prevalent at right arm. The ^{123}I-FP-CIT SPECT had normal uptake values, even if a reduction in left putaminal uptake was evident at visual inspection (Putamen/occipital uptake values: Put-L/Occ 3,94, Put-R/Occ 4,20). We decided to repeat the scan within one year as a follow up.

In all the three patients the mutation G1750A (p.Ala359Thr) in the exon 1 of *PEO1* gene was found. This mutation has been associated to a pure PEO phenotype [3] (Fig. 3).

Parkinsonism associated to *PEO1* gene has been described in few reports. A case of a 52 years old female with a levodopa responsive parkinsonism and the co-occurrence of POLG G848S substitution and Twinkle R334Q substitution was described for the first time

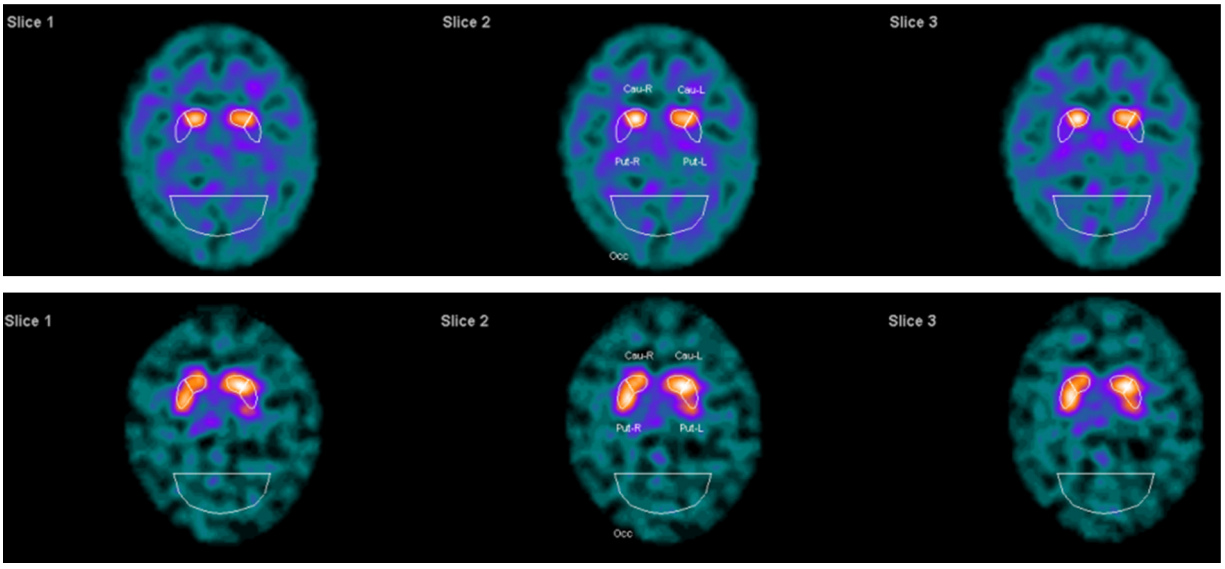

Fig. 2. ^{123}I-FP-CIT SPECT image of II-2 and III-1.