

Letter to the Editor

Cerebellar ataxia as atypical manifestation of the 3243A>G MELAS mutation

To the Editor:

The mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episode syndrome (MELAS) is defined by the presence of stroke-like episodes due to focal brain lesions often localized in the parieto-occipital lobes and lactic acidosis, and ragged red fibers (1). Ataxia can be observed in some patients. The 3243A>G substitution in the mitochondrial (mt) DNA tRNA^{Leu} (UUR) gene is by far the most frequent molecular etiology of MELAS. The genotype–phenotype correlation of the 3243A>G mutation is rather loose because the associated clinical manifestations are not restricted to cases with the full-blown MELAS syndrome. For instance, the 3243A>G mutation has been detected in patients with maternally inherited progressive external ophthalmoplegia, isolated myopathy, cardiomyopathy, or even in maternally inherited diabetes mellitus and deafness. We report on an Italian man with severe sporadic cerebellar ataxia as the presenting symptom of a MELAS mutation.

A 55-year-old man, who denied a positive family history of neurological diseases, presented a 10-year history of progressive speech and balance disturbances. The IQ of the patient was within the normal range. Neurologic examination revealed ataxic gait, dysarthric speech, and bilateral dysmetria on finger-to-nose. There was also mild proximal muscle weakness (4.5–5 using the Muscular Rating Scale) and hypotrophy in the upper limb girdle muscles. Proprioception and all sensory modalities were preserved. Blood routine examination, including lactate and creatine kinase content were normal. Electromyography was consistent with myopathic features in proximal upper and lower limb muscles. Brain MRI showed cortical and cerebellar atrophy (Fig. 1). Succinate dehydrogenase histochemical stain in a skeletal muscle biopsy showed numerous ragged blue fibers (RBF), of which the vast majority showed intense staining of cytochrome c oxidase (COX). Few muscle fibers were RBF/COX negative. Screening of the most common mtDNA alterations revealed the presence of the

3243A>G mutation. Using a described polymerase chain reaction–restriction fragment length polymorphism quantitative analysis and the endonuclease *Hae*III, we estimated mutant genomes at 40% in muscle and 8% in blood. No maternal relatives were studied.

Idiopathic late onset cerebellar ataxia represents about 50% of all forms of neurodegenerative ataxias in Italy (2). Using traditional clinical criteria (3), the diagnosis can be made after exclusion of other neurological conditions, such as tumors and multiple sclerosis, in the absence of family history. Recently, ataxia has been observed in several mitochondrial encephalomyopathies (coenzyme Q10 deficiency syndrome, neuropathy, ataxia, retinitis pigmentosa, myoclonus epilepsy and ragged red fibers, and Kearns–Sayre syndrome) (4). Furthermore, mitochondrial dysfunction as a primary cause of neuronal cell death for the vast majority of neurodegenerative diseases, including cerebellar ataxia, has been hypothesized (5).

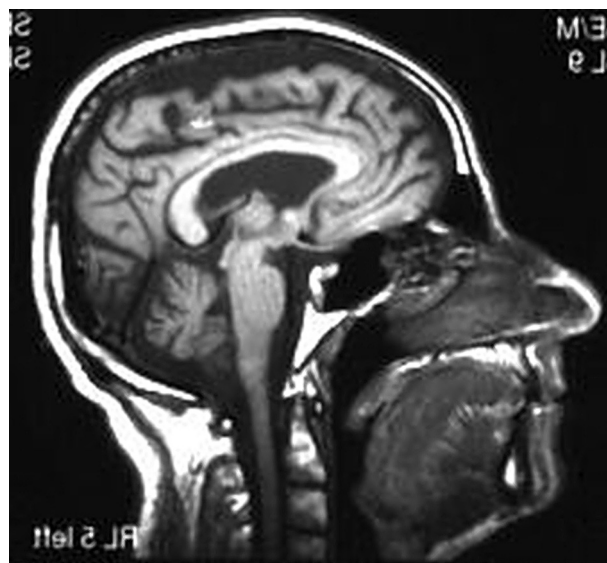


Fig. 1. Sagittal T1-weighted magnetic resonance imaging of the brain shows marked cortical and cerebellar atrophy.

The patient herein reported had long complained of symptoms related to his cerebellar disorder, but he did not manifest classical signs of the MELAS syndrome. The concurrence of muscle weakness and atrophy raised the suspect of mitochondrial involvement in the pathogenesis of cerebellar ataxia. MtDNA analysis in blood and muscle samples detected the 3243A>G mutation in relatively low abundance. It is tempting to hypothesize higher proportions segregating in the cerebellum or even locally in individual Purkinje cells. Single-fiber studies have showed that the pattern of intra-tissue segregation of mutant genomes may be more important than the absolute amount for the expression of the clinical phenotype (6, 7). Recent neuropathological studies in MELAS cases revealed diffuse atrophy of the cerebellar cortex, gliosis of cerebellar white matter, and cactus formation in Purkinje cells with mitochondria accumulation (8). Two extensive studies have assessed the relative frequency of the 3243A>G substitution in patients with sporadic ataxia (9, 10). Only one of 83 patients harboured about 8% of the mutation, but this was measured only in blood (10). Our findings emphasize the necessity to consider mtDNA alterations in the diagnostic ascertainment of cerebellar ataxia, after the exclusion of more obvious genetic causes.

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