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References


Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

Adult-Onset Myoclonus Ataxia Associated With the Mitochondrial m.8993T>C “NARP” Mutation

Mitochondrial dysfunction is an important cause of neurological disease. Mitochondrial disease can present at any age, and the clinical features are extremely varied. The
mitochondrial DNA (mtDNA) m.8993T>C mutation is usually encountered either in association with Leigh syndrome or the syndrome of neuropathy, ataxia, and retinitis pigmentosa. We describe severe, late-onset myoclonus ataxia related to the m.8993T>C mutation.

A 74-year-old man presented with a 3-year history of progressive hand clumsiness and poor balance. He was now wheelchair-bound and needed assistance in dressing, feeding, and washing. There was no history of seizures. He had a sister with diabetes mellitus and coeliac disease, but otherwise well. Family history was unremarkable for movement disorders and other neurological conditions. Both the patient and his sister had no children, and their mother who was deceased was an only child.

Clinical examination revealed bilateral, irregular, and multifocal myoclonus in both upper limbs, considerably aggravated by active movement. No pigmentary retinopathy was detected. Up-gaze was limited, but with intact smooth pursuit. Cognition was normal. Proximal (MRC 4/5) and distal (MRC 4+/5) muscle weakness was evident. Lower-limb reflexes were absent. Severe myoclonus ataxia rendered him unable to walk or stand independently.

Urea, liver function tests, creatinine kinase, serum lactate, vitamin E, blood copper, and coeruleoplasmin levels were unremarkable. Testing for anti-gliadin and anti-endomysial antibodies was negative.

Brain MRI revealed global cortical and cerebellar atrophy. Nerve conduction studies revealed a predominantly sensory axonal neuropathy. EEG did not reveal any epileptiform features. Photic stimulation evoked further myoclonic jerks associated with muscle activity artefact.

Fragile X–associated tremor ataxia syndrome and spinocerebellar ataxia types 1 to 3, 6, 7, and 17 were excluded; SGCE gene analysis was normal. Given that clinical features were suggestive of a mitochondrial disorder rather than other causes of myoclonus ataxia, common POLG mutations (p.Ala467Thr, p.Trp748Ser, and p.Gly848Ser) and mtDNA point mutations associated with MERRF (myoclonic epilepsy with ragged-red fibers) syndrome (m.8344A>C) were excluded; SGCE gene analysis was normal. Given that clinical features were suggestive of a mitochondrial disorder rather than other causes of myoclonus ataxia, common POLG mutations (p.Ala467Thr, p.Trp748Ser, and p.Gly848Ser) and mtDNA point mutations associated with MERRF (myoclonic epilepsy with ragged-red fibers) syndrome (m.8344A>G, m.8356T>C, and m.8363G>A) were excluded. Pyrosequencing of the MTATP6 and MTATP8 genes (methodology as described by Alston et al.3) revealed the m.8993T>C mutation in MTATP6 at 95% heteroplasmy in the patient’s blood and urine. The m.8993T>C mutation was undetectable in the respective samples from his sister, suggesting a sporadic mutation, although a maternal sample was not available to confirm this.

Myoclonus linked with ataxia is a common feature of the m.8344A>G MERRF mutation,4 and it has been reported with POLG mutations.5 Adult-onset ataxia and axonal neuropathy owing to the m.8993T>C mutation has been reported in a Finnish family,6 but severe myoclonus ataxia in association with the m.8993T>C mutation has not been previously reported.

The patient’s late symptom onset is remarkable. Clinical clues suggesting a possible late-onset mitochondrial disorder were the multisystem nature of the disorder and a phenotype characterized by myoclonus ataxia, neuropathy, and the mild up-gaze limitation. Cerebellar pathology and ataxia are common features of mitochondrial disease. Recently, the cerebellum has been implicated in the pathogenesis of cortical myoclonus.7 Apart from mitochondrial disease, myoclonus ataxia can be associated with many other conditions, such as coeliac disease, and various rare metabolic or genetic disorders.7 Mitochondrial disease related to the m.8993T>C mutation should be considered among adult patients who present with nondominant myoclonus ataxia, irrespective of age.

Legends to the Videos

Video 1. This video was taken at the age of 73 years. The sensitivity of the myoclonic jerks to photic stimulation is demonstrated during the EEG recording.

Video 2. This video was taken at the age of 74 years. The severe myoclonus ataxia is demonstrated during the finger-to-finger test and when trying to pick up a pen. On examination of the eye movements, smooth pursuit is intact, but there is evidence of marked upward gaze restriction. The head drop is owing to neck extensor weakness (MRC 4/5) rather than dystonia.

Mika H. Martikainen, MD, PhD,1 Grainne S. Gorman, MRCP, FRCP,1 Paul Goldsmith, MRCP,2 David J. Burn, FRCP,2 Doug M. Turnbull, FRCP,1 and Andrew M. Schaefer, MRCP1
1Wellcome Trust Centre for Mitochondrial Research, Newcastle University, Newcastle upon Tyne, United Kingdom
2Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, United Kingdom

References

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