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A case of ataxia and optic atrophy caused by NDUFA1 mutation

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Objective: To describe a novel association of a previously reported NDUFA1 mutation with slowly progressive sensory ataxia and optic atrophy.

Case description: A male born full-term from unrelated parents, had motor and speech developmental delayed acquisition and an IQ of 79. At the age of 5 he showed visual impairment, the fundus study showed an optic sub-atrophy. Brain MRI and MEP, both of which were unremarkable. At the age of 25 he was evaluated by a neurologist due to progressive gait instability. Neurological examination showed ataxic gait, positive Romberg sign, severely reduced visual acuity and pes cavus. Electroneurography documented sensory axonal polyneuropathy. Visual evoked potentials showed bilateral absence of P100. Lactate exercise test was positive, muscle biopsy was normal. Genetic tests for SCA 1,2,3,6,7 and FXN were negative. At 43 years old, he showed a worsening of balance. Second MRI, showed thinning of the optic nerves and slight vermian atrophy. The patient and his parents performed genetic testing through the Next Generation Sequencing Panel (Illumina), filtering results for genes associated to mitochondrial diseases.

Results: Genetic testing showed the hemizygous missense mutation c.55C>T; p.(Pro19Ser) on NADH-Ubiquinone Oxidoreductase Subunit A1 (NDUFA1) gene, which was inherited from his mother. To confirm pathogenicity, previous muscle biopsy testing by native blue gel electrophoresis showed a decrease in the enzyme activity of mitochondrial complex I. Gel electrophoresis showed a reduction in complex I subunits, especially NDUFA.

Conclusion: NDUFA1 codes for a subunit of CI and is fundamental for CI assembly and functioning [1]. The same mutation was previously described with young-onset Leigh syndrome [2]. Our case expands the phenotypic spectrum of NDUFA1 mutations, therefore should be considered among the causes of sensory ataxia with optic atrophy and further confirm the relevance of complex I for optic nerve integrity.

References:

[1] Janssen, R. J. R. J., Nijtmans, L. G., van den Heuvel, L. P. & Smeitink, J. A. M. Mitochondrial complex I: structure, function and pathology. J. Inherit. Metab. Dis. 29, 499–515 (2006).
[2] Fernandez-Moreira, D. et al. X-linked NDUFA1 gene mutations associated with mitochondrial encephalomyopathy. Ann. Neurol. 61, 73–83 (2007).