Movement disorders and cerebellar involvement in mitochondrial disorders

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Letter to the Editor

Recently, a paper about 50 patients with a genetically confirmed mitochondrial disorder (MID) who also presented with different types of movement disorders had been published by Schreglmann *et al.* [1]. We want to express some concerns and add some comments about this study.

MIDs not only manifest with movement disorders such as parkinsonism, dystonia, chorea, myoclonus, or ataxia, but also with athetosis, restless-leg syndrome, tics and Tourette syndrome, or tremor [2]. Athetosis has been particularly described in patients carrying mutations in the *WARS2*, *C10orf2* (manifesting as infantile onset spinocerebellar ataxia), and *ACO2* genes and in patients with Leigh syndrome. Restless-leg syndrome has been only occasionally reported as a manifestation of a MID. In a Gypsy female with mitochondrial multiorgan disorder syndrome (MIMODS), restless-leg syndrome was one among the multiple phenotypic features of the MID [3]. Restless-leg syndrome has been also found in a study of movement disorders in 678 MID patients from the UK [4]. In a study of 20 patients with genetically confirmed progressive external ophthalmoplegia, restless-leg syndrome, leading to sleep disturbance, was found in 35% of them. Tourette syndrome has been recently described in association with mutations in the nuclear-encoded

mitochondrial genes *MRPL3*, *DNAJC13*, and *OFCC1* respectively. Tics were one of the phenotypic manifestations of the m.3243A>G variant in an 11yo female with epilepsy and diabetes. Tremor in the absence of other parkinsonian features has been repeatedly reported in MIDs. Tremor is usually a non-dominant feature in MIMODS and associated with mutations in genes encoding for *tRNAs*, *COX15*, or *DGAT2*. The latter patient manifested additionally with Charcot-Marie-Tooth disease. Thus, we would like to know if the authors are aware of MID patients presenting with movement disorders other than the ones reported and if these MID patients were tested for mutations in genes mentioned above.

Multiple mtDNA deletions or mtDNA depletion may not only be associated with mutations in *POLG1*, *POLG2*, *C10orf2* (*TWINK*), and *SLC25A4*, but also in the *TFAM*, *RNASEH1*, *MGME1*, *DNA2*, *TK2*, *DGUOK*, *SUCLG1*, *SUCLA2*, *ABAT*, *RRM2B*, *TYMP*, *AGK*, *MPV17*, *OPA1*, *MFN2*, and *FBXL4* genes [5]. Which was the reason why these other nuclear genes were not tested for mutations in patients with multiple mtDNA deletions?

Cerebellar atrophy is not an unusual finding in MIDs. It is often associated with atrophy of the brainstem. Specific and non-specific MIDs may go along with cerebellar atrophy. In some patients with

a MID, cerebellar atrophy may be the dominant feature, whereas in other patients cerebellar atrophy may be a non-dominant feature of the phenotype. MIDs with dominant cerebellar atrophy include pontocerebellar hypoplasia type-6 and leukoencephalopathy with brainstem and spinal cord involvement and lactic acidosis [6]. Cerebellar atrophy as a non-dominant feature is caused by mutations in *tRNA*, *rRNA*, *AIFM1*, *MRPS22*, *ATAD3*, *ADCK3*, *COQ4*, *GFM2*, *RARS2*, *TTC19*, and *TWINK* genes respectively.

In summary, this interesting study could be more meaningful by discussing other types of movement disorders than the ones presented in association with MIDs, by testing patients with multiple mtDNA deletions for mutations in additional genes, and by a broader discussion of cerebellar atrophy in MIDs.

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