VIEWPOINT

Dystonia in ATP Synthase Defects: Reconnecting Mitochondria and Dopamine

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Four decades of research highlighted a significant role for mitochondrial dysfunction in the pathogenesis of movement disorders. A first milestone was set by the discovery that the neurotoxin *N*-methyl-4-phenylpyridinium (MPP^+), an apoptosis-inducing mitochondrial complex I inhibitor, induces parkinsonism by selectively damaging the substantia nigra.[1,2] This report sparked intensive investigations on the role of mitochondria in Parkinson's disease (PD),[3] fueled by the recognition of mitochondrial functions for several PD-associated genes.[2]

Sequencing of the mitochondrial genome was completed in 1981.[4] Reports linking mitochondrial DNA (mtDNA) variants to neurological phenotypes rapidly followed. Notably, two early works identified dystonia as a prominent feature of distinct mitochondrial syndromes,[5,6] leading to the speculation that "movement disorders might have a mitochondrial etiology".[7] The association between mitochondrial diseases and various movement disorders has been confirmed by several case reports and few larger series.[8-11] Nonetheless, systematic explorations of the underlying pathophysiological mechanisms are scarce.

Recently, independent studies elucidated a direct causal relationship between isolated dystonia and variants in genes encoding components of the mitochondrial ATP synthase (ATPase).[12,13] These remarkable findings encouraged us to reappraise the "mitochondria-movement disorder connection"[7] from a genetics-driven perspective. We posit that mild energetic failure caused by specific ATPase variants may influence the synaptic activity of several nodes of the motor circuits involved in dystonia pathogenesis. ATPase activity modulation driven by other genetic or environmental stressors may play a role in the functional network alterations seen in more common idiopathic dystonias.

Dystonia in Mitochondrial Diseases

Unique among the cellular organelles, mitochondria underlie a dual genomic control by both autochthonous mtDNA and the nuclear genome.[14,15] MtDNA encodes 13 subunits of the enzymatic complexes governing oxidative phosphorylation (OXPHOS) and 24 mitochondrial specific RNAs.[4] Further >1000 mitochondrial proteins are nuclear-encoded.[16] They are involved not only directly in OXPHOS, but also in respiratory chain-complex assembly, mtDNA replication, expression, and repair, as well as in other metabolic

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pathways.[15] Defects in any of these processes may result in a mitochondrial phenotype. Dystonia is a recurrently observed manifestation of mitochondrial diseases, particularly in pediatric cohorts.[8-11,17] In this setting, dystonia usually occurs within multisystemic phenotypes such as Leigh syndrome, a progressive encephalopathy associated with basal-ganglia necrotizing lesions.[18] Leigh syndrome presents in childhood, triggered by infection or other illnesses after an initial period of normal development.[19] Following metabolic crises, affected children develop various neurological symptoms including developmental regression, ataxia, and dystonia. Variants in several other mitochondrial genes (eg, *PMPCA*) present with a wide clinical spectrum ranging from relatively mild dystonic phenotypes to severe epileptic encephalopathies with movement disorders.[20] Additionally, dystonia is a key feature of rare mitochondrial syndromes such as Mohr-Tranebjaerg disease, along with deafness and optic atrophy.[6] Neurodegenerative diseases with a mitochondrial background may also feature dystonia as a part of their phenotype. In these cases, dystonia can precede other manifestations for several years[21] or outlast further more typical neurological signs.[22] Together, dystonia occurs in a variety of genetic defects linked to mitochondrial dysfunction, therefore, representing a rather non-specific manifestation, fitting the older definition of "secondary" dystonia within a broader phenotype. Isolated dystonia as clinical presentation of mitochondrial diseases is exceptional.[21]

ATPase: From Biochemistry to Clinical Phenotypes

OXPHOS is orchestrated by five multiprotein complexes located in the inner mitochondrial membrane. The first four complexes (I–IV), known as the respiratory chain, generate a transmembrane proton gradient by transferring electrons to molecular oxygen.[23] The fifth complex, referred to as ATPase, funnels this chemical force in the production of ATP.[24] ATPase consists of a globular F_1 head made of three αβ dimers and a membrane-embedded F_o subcomplex formed by a pore and a ring of multiple *c* subunits.[25,26] These two moieties are connected by a peripheral stalk and a central stalk. This peculiar structure enables ATP synthesis via a "chemomechanical" coupling.[27] Indeed, the proton influx through the F_o pore drives the rotation of the c-ring, which is transmitted via the central stalk to the catalytic F_1 sector, where the reaction $ADP + P_i \rightarrow ATP$ occurs.[28] Dimeric ATPase complexes assembly at the inner mitochondrial membrane in a modular fashion contributing to the shaping of mitochondrial cristae.[29] Only two of the 17 ATPase subunits are coded by mtDNA (*MT-ATP6* and *MT-ATP8*),[30] whereas the remaining ones are nuclear-encoded.[31]

ATPase defects are underrepresented among mitochondrial disease etiologies.[31] Beyond possible epidemiological considerations, this issue may be historically related to earlier difficulties in assaying complex V activity.[32,33] The group of Anita Harding in 1990 reported the first association between ATPase and human disease, by describing a *MT-ATP6* variant in a syndrome encompassing developmental delay, dementia, ataxia, and neuropathy.[34] The first disease-causing variant in a nuclear gene for ATPase, *ATP5F1E*, was reported 20 years later.[35]

ATPase and Dystonia: Early and Recent Evidence

Most ATPase-deficiency syndromes are clinically severe as expected by the cardinal role of the enzyme. *MT-ATP6* variants have been associated with Leigh syndrome.[36] Early-onset metabolic encephalopathies are also the main presentation of biallelic variants in genes encoding nuclear subunits (*ATP5F1A*, *ATP5F1D*, and *ATP5MK*).[37-40] In these settings, dystonia[41] and other movement disorders may be noticed after a stabilization of severe metabolic crises. An isolated ATPase-related movement disorder phenotype was observed for the first time in association with a heterozygous variant in *ATP5MC3*, which codes for the F_o ring *c*-subunit.[42] Neilson and colleagues[42] described a missense variant (p.Asn106Lys) in an autosomal dominant pedigree in which several relatives displayed either childhood-onset generalized dystonia or adult-onset spastic paraplegia. Several members also displayed isolated focal limb or neck dystonia. Notably, the same p.Asn106Lys variant was found as a de novo event in a nonrelated 11-year-old boy suffering from isolated upper-limb dystonia.[42] Following this report, further observations expanded the association between ATPase defects and dystonia. Zech et al[13] described a heterozygous *ATP5MC3* missense variant in a 15-year-old girl with developmental delay and dystonia. The same group confirmed the role of *ATP5F1E* as a mitochondrial disease gene by describing homozygous variants in independent patients who developed limb/generalized dystonia after the stabilization of metabolic crises. Furthermore, they expanded the inheritance pattern and phenotypes associated with variants in *ATP5F1A*, the gene encoding the α-subunit of the globular F_1 subcomplex.[13] Biallelic *ATP5F1A* defects were previously described in two infants with fatal neonatal encephalopathy.[13] Zech et al[13] reported de novo heterozygous *ATP5F1A* variants in two non-related children with a dystonic cerebral-palsy phenotype and in a third proband with failure-to-thrive and lactic acidosis in the first months of life, who subsequently recovered and had no persistent neurologic phenotype. Finally, they individuated *ATP5PO*, encoding the peripheral stalk subunit OSCP,

as a new gene linked to epileptic encephalopathy and dystonia.[13]

The latest association between ATPase defects and dystonia was described in two families with heterozygous missense variants in *ATP5F1B*, coding for the β-subunit of the F_1 catalytic sector. In affected individuals, age at dystonia onset ranged from infancy to adolescence. Dystonia began in a limb and showed a different rate of progression, but all affected individuals retained independent gait and showed no additional neurological features.[12] Non-affected relatives also carried the *ATP5F1B* variant, pointing to a reduced penetrance mechanism. Intriguingly, *ATP5F1B* had been associated with human disease in a single previous report. Here, a de novo missense variant affecting a nearby amino acid was the cause of a severe congenital mitochondrial uncoupling syndrome.[43] Table 1 summarizes ATPase defects associated with dystonia.

Mechanistic Insights

Several mechanisms drive the pathogenicity of ATPase variants.[44] A constant biochemical feature is the reduction of ATPase enzymatic activity, whose extent may correlate with phenotypic severity.[13,42] In metabolic encephalopathies caused by biallelic variants, the protein levels of ATPase are invariably reduced.[37,38,40] This finding is accompanied by alterations of cristae morphology.[37,40] Conversely, ATPase levels as well as gross mitochondrial morphology are mostly preserved in dominant ATPase disorders.[12,13] In this setting, the reported missense variants mostly alter highly conserved amino acids in interhelical or intersubunit contact areas of the affected proteins, suggesting a possible dominant negative effect of the mutant subunits. Interestingly, in *ATP5F1B*-related isolated dystonia, ATPase levels are even slightly increased and assemble in larger oligomeric structures.[12] This phenomenon might reflect an attempt of functional compensation, because dimerization and oligomerization regulate ATPase enzymatic efficiency.[45] Notably, *ATP5F1A* and *ATP5F1B* display high predicted constraints against both missense and loss-of-function variants (see Table 1). Therefore, it cannot be ruled out that haploinsufficiency may also be a pathogenic mechanism in some ATPase defect-related disorders, although direct evidence is currently lacking.

TABLE 1 *Nuclear ATP synthase genes recently associated with dystonia are reported along with the detected variants and corresponding references*

Gene	*ATP5F1E*	*ATP5PO*	*ATP5F1A*	*ATP5MC3*	*ATP5F1B*
Variant (s)	c.35A > G (p.Tyr12Cys)	c.34C > T (p.Gln12*) c.329-20A > G	c.545G > A (p.Arg182Gln) c.1037C > T (p.Ser346Phe)	c.318C > G (p.Asn106Lys) c.319C > G (p.Pro107Ala)	c.1000A > C (p.Thr334Pro) c.1445 T > C (p.Val482Ala)
Inheritance	AR	AR	AD/de novo	AD/de novo	AD incomplete penetrance
pLI score	0.01	0.06	1	0.26	0.98
Missense *z*-score	−0.17	0.03	2.44	1.02	3.17
Reported families	2	1	2	3	2
References	Zech et al[13]	Zech et al[13]	Zech et al[13]	Neilson et al[42]; Zech et al[13]	Nasca et al[12]
Dystonia features	Non progressive limb dystonia/ generalized dystonia	Early onset dystonia	Dystonic cerebral palsy	Childhood-onset, progressive generalized dystonia/isolated upper limb dystonia	Early-onset isolated and slowly progressive dystonia
Non dystonia features	Developmental delay, lactic acidosis, metabolic crises, ataxia, peripheral neuropathy	Developmental delay, epilepsy, hypotonia, microcephaly, increased CSF lactate	Developmental delay, spastic paraparesis, ataxia, increased blood lactate	Spastic paraplegia in adult relatives	–

Abbreviations: AR, autosomal recessive; AD, autosomal dominant; pLI, probability of being loss-of-function intolerant, according to gnomAD (https://gnomad.broadinstitute.org/); CSF, cerebrospinal fluid.

Subunits coded by *ATP5F1A*, *ATP5F1B*, and *ATP5MC3* are present in multiple copies in the functioning ATPase. The relative expression of the mutated gene likely contributes to the variable clinical expression and incomplete penetrance of milder phenotypes. Differential expression of mutated genes as well as of subunit homologues may be in turn shaped by stressors and other environmental factors.

Oxygen consumption rate is variably reduced in severe recessive phenotypes,[13] whereas it is normal in *ATP5F1B*-related isolated dystonia.[12] The opposite alteration, namely a significant increase in oxygen consumption rate is the hallmark of the allelic *ATP5F1B*-associated uncoupling syndrome.[43] This is the consequence of a proton gradient dissipation without parallel generation of ATP through defective ATPase.[43]

Reconnecting Mitochondria to Dopaminergic Transmission

Genetic, imaging, and functional studies[46,47] highlighted the involvement of multiple pathways in the pathophysiology of dystonia. Several of these biological processes eventually converge in a dysfunction of basal ganglia and dopaminergic neurotransmission. Notably, dystonia in Leigh syndrome is accompanied by striatal lesions.[19] An obvious structural damage is, however, missing in ATPase defect-related isolated dystonia.[12] The net biological consequences of ATPase defects may quite differ from those of respiratory chain defects (for an overview of associated clinical syndromes see Goldstein et al and Zeviani and Viscomi).[32,48] In dopaminergic cells, complex I–IV defects impair ATP production, increase reactive oxygen species (ROS) formation, and induce cell death. A selective functional inhibition of ATPase results in ATP depletion, but not in enhanced ROS production or apoptosis.[49] A slightly less efficient energy supply may produce a relevant functional disturbance in susceptible networks. Among the monoaminergic systems, a peculiarity of the dopaminergic neurons resides in the intrinsic cytotoxicity of dopamine, because its metabolism via monoamine oxidase may produce ROS.[50,51] Graves et al[51] showed that in the dopaminergic terminals, radicals produced by monoamine oxidase do not increase oxidative stress, but are shuttled in the respiratory chain entering at complex IV as electron donor and contribute to ATP production (see Fig. 1). Here, the application of the F_o subunit inhibitor oligomycin induces dropping of dopamine release. This ROS recycling system may on one hand limit autoxidation and on the other hand drive the additional ATP generation needed for the phasic firing of dopaminergic neurons.[51,52] This tenuous balance may be easily disrupted (eg, if ATPase efficiency decreases). This hypothesis might be tested experimentally by expressing a known pathogenic ATPase variant in the same setting

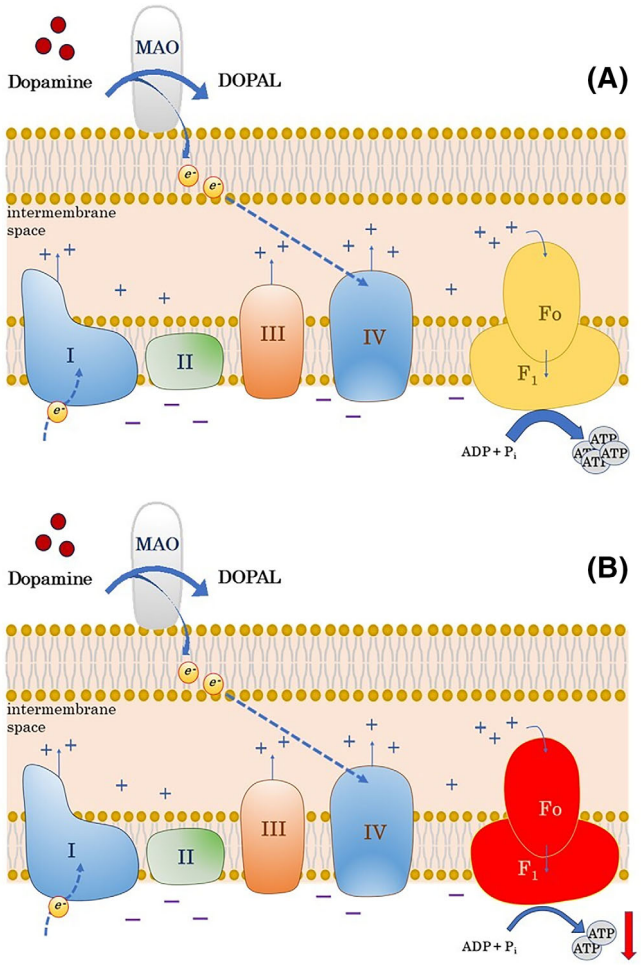

FIG. 1. Possible impact of ATPase defects on dopaminergic transmission. (**A**) In dopaminergic axons, electrons generated by dopamine metabolism via monoamine oxidase (MAO) are shuttled in the respiratory chain via complex IV.[51] (**B**) A mild ATPase defect (eg, caused by a heterozygous *ATP5F1B* variant) may limit the efficiency of this "recycling" process. [Color figure can be viewed at wileyonlinelibrary.com]

(see Fig. 1) and in turn by exploring the link with a dystonic phenotype (eg, in a murine model). Indeed, a semicritical dopaminergic deficit may clinically manifest as dystonia. Interestingly, in a murine model of dopa-responsive dystonia, several mitochondrial proteins were upregulated in the striatum, including the key F_1-rotor subunit *ATP5F1C*.[53] This event could represent a compensatory mechanism to defective dopamine biogenesis and inefficient dopaminergic firing.

From a broader perspective, mild energetic failure caused by specific ATPase variants may result in widespread functional changes in several other neuronal circuits (striatal, cortical, and cerebellar) known to be involved in the pathogenesis of dystonia.[46,47] In this setting, fluctuations in energy supply may directly influence the synaptic activity or lead to compensatory changes that eventually result in abnormal synaptic plasticity and aberrant neuronal firing mechanisms, which have been linked to the pathogenesis of dystonia in several animal

models.[46,47] The synaptic impairment in multiple pathways might explain a lacking response to levodopa therapy in *ATP5F1B*-related isolated dystonia.[12] It furthermore highlights the unmet need for an overarching therapeutic target with broader modulatory effect on synaptic activity in dystonia-relevant circuits.

The Second Hit Paradigm

Several classical forms of monogenic dystonia display reduced penetrance. Affected subjects become symptomatic early in life, whereas asymptomatic carriers are not expected to convert beyond the third decade (eg, in *TOR1A*-related dystonia).[54] These peculiarities suggest a relevant role for extragenetic stressors in the pathophysiology of dystonia. According to the second-hit hypothesis, the "first" genetic alteration underlies maladaptive synaptic plasticity and requires additional genetic or environmental factors to become clinically manifest.[55] Alternatively, a compensation via endogenous protection factors may play a role.[55] The interplay between genetics and stressors may be especially detrimental in a defined time-window of neurodevelopment. This may explain the age-dependent susceptibility to develop a movement disorder phenotype as well as its specific manifestation (eg, dystonia or spastic paraplegia in childhood- vs. adult-onset *ATP5MC3*-related disease). ATPase defect-related isolated dystonia recapitulates the incomplete penetrance and age-dependent onset of other monogenic dystonias. This suggests that additional modifiers may shape the net biological effect of otherwise mild or potentially compensated ATPase defects. In respect to autosomal recessive ATPase defect-related disorders, it may also be interesting to explore the presence of an endophenotype in heterozygous carriers.[56]

Conclusions

Two phenotypic clusters associated with ATPase defects are emerging. Recessive forms underlie multisystemic phenotypes in which non-progressive dystonia becomes evident after an early period of metabolic crises or worsening encephalopathy. Some dominant pedigrees feature isolated dystonia with incomplete penetrance. The cardinal role of ATPase in energy metabolism makes clear that even slight disturbances entail relevant functional alterations. Therefore, the association of ATPase defects with early-onset severe encephalopathies and uncoupling syndromes is not surprising. In these complex pictures, the detection rate of dystonia may be poor.[57] We posit that ATPase defects underlie a much larger number of phenotypes also featuring dystonia, warranting reverse phenotyping in diagnosed cases. Monogenic disorders offer unique insights into the pathophysiology of phenotypically related sporadic conditions. The history of neurogenetics in PD exemplifies this notion. The discovery of α-synuclein variants in familial PD[58] preceded the protein identification in Lewy bodies,[59] and thereafter, contributed to its recognition as central etiological substrate in sporadic PD. Such strong overarching paradigm is missing in dystonia. The recent delineation of ATPase-related dystonias reawakes our endeavor to fulfill this unmet goal. Indeed, the exceptional association of certain ATPase defects with an exquisite dystonia phenotype with incomplete penetrance highlights the vulnerability of specific neuronal circuitries to this event and the likely role of cofactors. Dissecting the molecular basis of these ATPase defects may, therefore, help to shed light on the pathophysiology of common idiopathic dystonias. ●

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Data Availability Statement

Not applicable.

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