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The Neurodegenerative Mitochondriopathies

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Abstract

Mitochondria are physically or functionally altered in many neurodegenerative diseases. This is the case for very rare neurodegenerative disorders as well as extremely common age-related ones such as Alzheimer's disease and Parkinson's disease. In some disorders very specific patterns of altered mitochondrial function or systemic mitochondrial dysfunction are demonstrable. This review classifies neurodegenerative diseases using mitochondrial dysfunction as a unifying feature, and in doing so defines a group of disorders called the neurodegenerative mitochondriopathies. It discusses what mitochondrial abnormalities have been identified in various neurodegenerative diseases, what is currently known about the mitochondria-neurodegeneration nexus, and speculates on the significance of mitochondrial function in some disorders not classically thought of as mitochondriopathies.

Keywords

Alzheimer's disease; cybrid; mitochondria; mitochondriopathy; Parkinson's disease; neurodegeneration; neurodegenerative

1. The neurodegenerative mitochondriopathies

Neurodegenerative diseases are clinically characterized by insidious onset and chronic progression. Neuronal populations of the peripheral nerves, spinal cord, or brain functionally fail and die. Neuroanatomically localizable functional impairment and neurodegeneration associate with recognizable syndromes that are ideally distinct, although in clinical and even neuropathologic practice substantial overlap exists. Neurodegenerative disease clinical syndromes are often categorized by whether they initially affect cognition, movement, strength, coordination, sensation, vision, or autonomic control.

Although the word "neurodegenerative" implies neuronal loss causes disease, it is possible neuronal demise is merely the final stage of a preceding period of neuron dysfunction. From an etiologic standpoint, it seems reasonable to approach these disorders from the perspective that neurodegeneration itself does not cause disease, but rather the physiologic event or events that cause neurodegeneration to occur do. In the case of autosomal dominant, recessive, or matrilineal neurodegenerative disorders the primary event can be obvious. With sporadic disorders it is typically less clear. It is also far more difficult for laboratory-based investigators to model non-Mendelian neurodegenerations. Because of this, there is a tendency to de-emphasize the fact Mendelian and sporadic disorders that share a common name may potentially represent distinct entities.

Mitochondrial dysfunction can both drive and mediate human disease. The first time mitochondrial dysfunction was identified to play an important role in disease was during the early 1960's, when a woman with thyroid-independent hypermetabolism was reported [1]. By the 1980's, a large number of rare metabolic disorders with dysfunction of an enzyme or enzymes located within mitochondria were recognized [2]. During this period, advancing knowledge of mitochondrial genetics also allowed investigators to identify several rare disorders as likely arising from mutation of mitochondrial DNA (mtDNA). These disorders typically affected the central nervous system, causing encephalopathy, and muscle, causing weakness. In the late 1980's and early 1990's, specific mutations of mtDNA were indeed shown to cause a number of these maternally inherited "encephalomyopathy" diseases [3–7].

Around this time it was shown mitochondrial dysfunction also occurred in neurodegenerative diseases with non-mitochondrial etiologies. For example, even though Huntington's disease (HD) is caused by expression of abnormal huntingtin protein, mitochondrial dysfunction is felt by many to play an important role in this disorder's development and progression [8,9]. While it is not yet exactly clear how mutant huntingtin causes mitochondrial dysfunction, it is reasonable to presume huntingtin mutation ultimately causes mitochondrial dysfunction in HD. In some neurodegenerative diseases with mitochondrial dysfunction, though, no clear upstream pathology has been elucidated. Regardless of whether mitochondrial dysfunction is a primary cause of neurodegeneration, a mediator of neurodegeneration, or an epiphenomenon, some propose defining neurodegenerative diseases with recognized mitochondrial dysfunction as "neurodegenerative mitochondriopathies" [10].

2. Neurodegenerative mitochondriopathies with clear maternal inheritance

2.1 Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy (LHON) is a well recognized, well characterized neurodegenerative disease [11]. This relatively common cause of usually presenile vision loss was first described in 1871 [12]. Clinical vision loss proceeds over weeks to months, and is believed to reflect the presence of metabolic "crisis" on top of baseline aerobic compromise. As is the case with more common neurodegenerative diseases there is anatomically focal neurodegeneration; LHON is characterized by neurodegeneration of the ganglion cell layer and optic nerve. Retinal ganglion cell degeneration, interestingly, is also seen in an autosomal dominant neurodegenerative mitochondriopathy associated with defective mitochondrial fusion [13]. The primary cause of LHON, though, is mitochondrial DNA (mtDNA) mutation. Three particular mutations in mtDNA genes that encode complex I subunits account for the majority of LHON [14].

Disease penetrance is greater in men than women. Perhaps for this reason, although LHON is clearly an mtDNA-derived disease and exclusively maternally inherited, the majority of affected individuals have no apparent family history [15]. Strikingly obvious matrilineal kindreds are nevertheless known. Studies of these kindreds dominated early research into this disorder, and until it was recognized that mtDNA is maternally inherited LHON was postulated to result from a latent intrauterine infection [16]. In 1988, the first LHON mutation was demonstrated in a large Australian kindred with clear maternal inheritance [17]. In 1989, complex I dysfunction in platelet mitochondria from members of a different matrilineal LHON kindred was shown [18]. As is the case with more common neurodegenerative diseases, although there is anatomically focal neurodegeneration the mitochondrial defect is not limited to neurons or the nervous system. It is presumed anatomic selectivity is partly a consequence of the high metabolic demands of the target tissue and perhaps other unique structural or physiologic variables [11].

Because the upstream cause of mitochondrial dysfunction in LHON is known, it is commonly believed studying LHON could potentially elucidate the role of mitochondrial dysfunction in other neurodegenerative mitochondrialopathies. Because LHON mutations are typically homoplasmic or high percentage heteroplasmies, and because their disease association is so well established, cytoplasmic hybrid (cybrid) modeling has long been and remains the gold standard for mechanistic-oriented LHON investigation [19–34].

Cybrids are cell lines created by placing mitochondria from individual human subjects into cultured cells (Figure 1). Cybrids are also useful for assessing the integrity of an individual's mitochondrial genes, because when the individual's mitochondria are transferred the genes inside those mitochondria are also transferred. The mitochondria moved into the cultured cells are grown inside the cells until there are enough to study. LHON cybrid studies typically reveal reduced complex I-dependent oxygen consumption, reduced ATP production, oxidative stress, and a pro-apoptotic shift in basal apoptotic set points. Reduced complex I activity has been occasionally but not consistently observed. No LHON animal model currently exists.

2.2 The encephalomyopathies

Several other rare mitochondrialopathies are clearly caused by mtDNA mutation, show maternal inheritance, and are associated with neurodegeneration [35]. It is therefore reasonable to consider them neurodegenerative mitochondrialopathies. These disorders include the mitochondrial encephalopathy, lactic acidosis, and strokelike-episodes (MELAS) syndrome, the myoclonic epilepsy with ragged red fibers (MERRF) syndrome, the Kearns-Sayre syndrome (KSS), maternally inherited Leigh syndrome (MILS), and the neuropathy, ataxia, and retinitis pigmentosa (NARP) syndrome.

MELAS neurodegeneration involves the cerebellar purkinje layer and cortical neurons. Cortical territories in the occipital and parietal lobes are preferentially affected [36]. MERRF neurodegeneration involves the cerebellar purkinje layer and dentate nucleus. In at least some patients degeneration of pallidoluysian, spinal cord, substantia nigra, inferior olivary nucleus, locus ceruleus, and pontine tegmentum neurons has also been reported [37]. In addition to spongy degeneration of the white matter, KSS can associate with neurodegeneration of the cerebellum (especially purkinje cells) and brainstem nuclei [38]. Brain regions affected in MILS include the brainstem, basal ganglia, thalamus, optic nerves, and spinal cord neurons; frank isolated neuronal loss, though, may be limited. Neuropathologic studies of NARP are rare, but one study reported visual, auditory, and olfactory pathway neurodegeneration in conjunction with cerebellar purkinje cell, dentate nucleus, inferior olive, and putamenal degeneration [39].

A detailed description of these classic encephalomyopathy disorders is beyond the scope of this review, although several points are worth making. Their age of onset is relatively young. In particular, MILS tends to manifest at a very young age. Non-nervous system tissues such as muscle may be prominently affected. Unlike LHON, the mtDNA mutations that cause these disorders are generally heteroplasmic. The anatomic pattern of neurodegeneration is also less restrictive than that of LHON. MELAS, MERRF, and KSS mutations appear to reduce levels of ETC enzymes, and occur in conjunction with mitochondrial proliferation. MILS and NARP, which are caused by mutations in an mtDNA-encoded ATP synthase subunit, do not reduce levels of ETC enzymes and are not associated with mitochondrial proliferation.

3. Predominantly sporadic neurodegenerative mitochondrialopathies

3.1. Alzheimer's disease

AD is the most common neurodegenerative disease. The typical course is progressive cognitive decline with prominent amnesia. Risk increases dramatically with advancing age, and among

those over 85 years old nearly half are affected [40]. The commonality of AD in the very old begs the question of whether AD in this demographic is truly a disease or rather an undesirable consequence of aging [41]. As the disease progresses, neurodegeneration becomes increasingly pervasive. There is consensus that degeneration begins in medial temporal structures, including layer 2 of the entorhinal cortex and various hippocampal substructures [42]. Neurons that form the perforant pathway, which connects the entorhinal cortex with the dentate gyrus, are affected early on. Hippocampal CA1 neuronal integrity may define a border between symptoms and no symptoms; aged individuals with CA1 neuron loss are much more likely to have clinical dementia than those who do not [43,44]. At intermediate stages cortical association area neurons of the temporal and parietal lobes degenerate. Loss of basal forebrain neurons follows.

AD is often divided into early versus late onset forms, and autosomal dominant versus non-autosomal dominant forms. Autosomal dominant AD, with rare exceptions, typically presents before the age of 65. Mutations in the amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) genes cause autosomal dominant AD and appear to alter processing of APP towards the 42 amino acid beta amyloid (A β) derivative [45]. A β is the major constituent of amyloid plaques found in the brains of elderly individuals with and without AD. Accordingly, an “amyloid cascade hypothesis” proposes AD is primarily a consequence of abnormal APP processing to particular A β variants, which then behave in a toxic fashion [46,47].

If A β does induce neurodegeneration, the mechanism may involve mitochondrial interference. In support of this, isolated mitochondria exposed to A β have diminished respiratory capacity and cytochrome oxidase inhibition [48,49]. Cells depleted of endogenous mtDNA (p0) cells, which lack functional electron transport chains (ETC), are impervious to A β [50]. Transgenic mice expressing mutant APP genes show altered mitochondrial function, and early increased expression of genes encoding mitochondrial proteins and ETC subunits is seen in an AD transgenic mouse line [51]. Transgenic mice show physical associations between mitochondria and A β as well as between mitochondria and APP [52–56].

Brain mitochondria are clearly altered in persons with AD. There is agreement that human AD brains contain reduced numbers of normal mitochondria [57,58]. When abnormal appearing and degrading mitochondria are taken into account, though, AD brain mitochondrial mass may actually be increased [58]. Physical association between mitochondria and A β also occur in human AD [59–61]. Physical interactions between presenilin 1 (PS1) and mitochondria are additionally reported [62].

V_{max} activities of several enzymes located within mitochondria are reduced in AD [63]. These include pyruvate dehydrogenase complex, alpha ketoglutarate dehydrogenase complex, and complex IV (cytochrome oxidase; CO) of the mitochondrial ETC. CO constitutes the terminal end of the ETC. It accepts electrons from cytochrome c, which receives them from more upstream parts of the chain. It contains 13 protein subunits. Ten are encoded by nuclear and three by mitochondrial DNA (mtDNA) genes.

The AD CO V_{max} activity reduction was first shown in platelets in 1990 and brain in 1992 [64,65]. Anatomic distribution of the CO defect was initially debated; it is now accepted to occur at least in platelets, fibroblasts, and large parts of the brain [63]. Reports using different experimental methods suggest CO activity in AD subjects is 10–50% less than in age-matched controls. In general, studies that isolate mitochondria report bigger reductions than studies that do not. CO reduction occurs at all stages of the disease, including mild cognitive impairment (MCI) [63,66].

Because CO activity is reduced outside the brain it presumably is not a neurodegeneration artifact. Whether the V_{max} reduction reflects reduced CO enzyme or a structurally altered

enzyme is still debated [63]. The Vmax activity rate is reduced in tissue homogenates normalized to total cell protein, in highly purified mitochondrial fractions in which the activity rate is normalized to total mitochondrial protein, and when normalized to activity of the mitochondrial enzyme citrate synthase. Spectral analysis of the enzyme finds it is kinetically altered in AD and lacks one of its two substrate binding sites [67]. Studies report AD brains have increased CO immunochemical staining and CO gene expression [58,68]. All this supports the view CO activity is reduced in AD because the enzyme is structurally different than it is in controls. Other studies, though, report CO protein levels and mRNA levels for several CO genes are reduced in AD and support the possibility CO activity is reduced because there is less CO [69,70]. Perhaps both scenarios occur.

Cybrid studies suggest mtDNA is at least partly responsible for reduced CO activity in AD [71]. Cybrid studies show mitochondria obtained from platelets of persons with AD have reduced CO activity [72]. This specific biochemical defect persists over time in the cybrid lines, which supports the view mtDNA differs between AD and control subjects and that these differences can affect CO. AD cybrid cell lines containing AD subject mitochondria/mtDNA also overproduce free radicals and A β [72,73]. Although some studies find specific sequence-level differences between AD and control subject brain mtDNA, it is not clear such differences also occur in cybrids [72,74]. The jury is still out on exactly how mtDNA from AD subjects differs from that of controls.

Data from epidemiologic, neuropsychological, and biomarker studies also suggest mitochondrial inheritance could influence AD risk and pathology. One study found for AD subjects with a demented parent the demented parent was more often the mother [75]. This relationship persisted after correcting for greater female longevity, and implies having an AD mother confers a greater risk of AD than having an AD father. At least some gene association studies suggest mtDNA haplogroups influence AD risk [76]. A large analysis of Framingham study subject offspring (the Framingham Offspring Study) found neuropsychological test performance in non-demented, middle aged individuals with an AD-affected mother was deficient relative to those with an AD-affected father or no AD-affected parent [77]. This may or may not reflect a presymptomatic AD carrier state. Positron emission tomography (PET) studies are relevant to this question. PET quantifies brain glucose utilization and reports this as a “cerebral metabolic rate of glucose” (CMR_{glu}). AD subjects have reduced CMR_{glu} in particular brain regions [78–80]. Cognitively intact, middle aged individuals with AD mothers but not AD fathers also have AD-like patterns of CMR_{glu} reduction [81].

Evidence suggesting mitochondria in general and CO specifically influence AD risk and histopathology has been used to justify a “mitochondrial cascade hypothesis” for AD. In the mitochondrial cascade hypothesis, mitochondria sit at the apex of AD histopathology and neurodegeneration (Figure 2) [74,82]. Many investigators, though, feel mitochondrial dysfunction in AD represents a downstream event and plays at most a minor role in the disease. At least one critical pro and con discussion of this controversial topic is available to those interested in this debate [63].

3.2. Parkinson's disease

PD is the most common neurodegenerative movement disorder and its prevalence rises with age. 1–3% of those over 80 are affected [83]. Neuron loss is particularly profound in the substantia nigra pars compacta, although early neurodegeneration also occurs in other discrete brainstem and basal forebrain nuclei. Surviving nigral neurons may contain intracytoplasmic inclusions called Lewy bodies. While Lewy bodies are not restricted to the substantia nigra, the presence of nigral Lewy bodies establishes the histologic diagnosis.

The classic clinical signs of resting tremor, bradykinesia, cogwheel rigidity, and postural instability are associated with loss of substantia nigra dopaminergic neurons. Like AD, PD is clinically partitioned into early and late onset variants and Mendelian versus non-Mendelian variants. The percentage of Mendelian cases declines with advancing age, while the percentage of non-Mendelian cases increases.

In the 1980's the MPTP story catapulted mitochondria to the forefront of PD research [84, 85]. A group of narcotic abusers in the San Francisco area developed parkinsonism after using meperidine contaminated with the chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). It was subsequently shown MPTP is converted to a derivative, 1-methyl-4-phenylpyridinium (MPP+), which inhibits complex I of the mitochondrial ETC [85]. Epidemiologic studies also suggest mitochondria-toxic pesticides may increase PD risk [86, 87]. Investigators have extensively used MPTP and a commercially available complex I inhibitor, rotenone, for cell culture and animal modeling of PD [88].

In 1989, complex I activity was shown to be reduced in persons with idiopathic PD [89–91]. Activity is reduced in multiple tissues, including substantia nigra, frontal cortex, platelets, muscle, and fibroblasts and so it is probably a systemic event [92,93]. Potential explanations for the PD complex I defect include exposure to exogenous inhibitors, systemic endogenous production of an inhibitory factor, or mtDNA-encoding of complex I subunits [94].

Seven of the suspected 46 complex I subunits are mtDNA-encoded. It was hypothesized in 1989 that because mtDNA contributes so importantly to complex I structure and function, and because mtDNA abnormalities can produce sporadic disease, mtDNA was the most likely cause [89]. This hypothesis was tested using cybrids, and to date multiple groups using cybrids with human neuroblastoma, teratocarcinoma, or adenocarcinoma nuclear backgrounds report PD cybrid cell lines have reduced complex I activity [95–97]. In addition to reduced complex I Vmax activity, these cell lines have increased reactive oxygen species production, reduced mitochondrial calcium storage, and cytoplasmic α -synuclein aggregations. The actual mtDNA alterations that account for this are unknown. It was recently reported mutations clustered within a particular stretch of the mtDNA ND5 gene are present in the brains of PD but not control subjects [98,99]. While such mutations are present in very low abundance in brain tissue, the possibility these mutant clones are concentrated within nigral neurons has not been ruled out. Deletions also concentrate in nigral neurons, where they can comprise a substantial percent of the total mtDNA [100,101]. Whether or not such mtDNA abnormalities occur in PD cybrid cell lines has not been reported.

If mtDNA does influence PD risk, it is necessary to consider whether inherited polymorphisms, inherited mutations, or somatic mutations are most relevant. Several lines of investigation support a role for mtDNA inheritance. Epidemiologic studies find for non-Mendelian cases that nevertheless have a PD-affected parent, the affected parent is more likely to be the mother [102,103]. Mitochondrial haplogroup and polymorphism association studies suggest mtDNA variation alters PD risk [94,104]. The systemic nature of the PD complex I defect supports the view mtDNA inheritance is more important than somatic mutation acquisition.

A variety of autosomal dominant and recessive forms of Mendelian PD are now defined. Mitochondrial dysfunction is implicated in several variants. One cause of autosomal dominant PD is mutation of the α -synuclein gene, and Lewy bodies consist largely of fibrillar α -synuclein. Complex I inhibition promotes α -synuclein aggregation in cell culture and PD animal models [105–107]. Other genes implicated in Mendelian PD encode proteins that localize to mitochondria or influence mitochondrial physiology. Examples of such proteins include parkin, DJ1, PINK1, and LRRK2. This convergence upon mitochondria suggests at the very least mitochondria initiate a final common pathway of neurodegeneration.

3.3. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is characterized by progressive weakness that arises from upper and lower motor neuron degeneration [108]. ALS is more common in those over 50 years of age and in men. It is relatively rare, with a prevalence that is well below 1% of the population. Similar to AD and PD, both sporadic and Mendelian forms exist, and with increasing age the proportion of those with Mendelian inheritance declines. The most studied Mendelian form of ALS is caused by mutation of the superoxide dismutase 1 (SOD1) gene on chromosome 21. SOD1 mutation reportedly accounts for approximately 2% of ALS cases.

Perturbations of mitochondrial ultrastructure in ALS were revealed several decades ago [109]. Although ALS neurodegeneration is anatomically specific, mitochondrial abnormalities have also long been noted in non-degenerating sensory neurons as well as outside the nervous system [110,111]. Cytoplasmic inclusions (Bunina bodies) that may represent mitochondria-containing autophagic vacuoles are observed in ALS motor neurons [112–114].

During the 1990's functional studies of ALS mitochondria were reported. Calcium levels in motor neuron synaptic terminals of ALS subjects were found to be elevated despite increased numbers of local mitochondria, suggesting a defect of mitochondrial calcium sequestration [115]. Increased complex I activity was seen in an individual with familial ALS [116]. Reduced cytochrome oxidase activity was shown in sporadic ALS patients [117]. Based on Parker's mtDNA-based model of sporadic disease, cybrids were used to study mitochondria obtained from ALS subject platelets. Cybrids produced on a neuroblastoma nuclear background showed a significant reduction in complex I activity and non-significant trends towards reduced complex III and IV activities [118,119]. A sporadic ALS reduction in complex I activity was corroborated by subsequent studies of ALS muscle, and muscle also revealed evidence of mtDNA perturbation [120,121]. ETC activities were reduced and mtDNA altered in ALS spinal cord [122]. In further regard to the question of whether mtDNA is relevant to ALS, in one registry of ALS individuals with an ALS-affected parent age of onset was influenced when the mother but not the father also had the disease, and there were more affected mothers than fathers [123]. Mitochondrial DNA haplogroups also appear to influence ALS risk [124].

ALS is typically modeled using rodents that express human mutant SOD1. SOD1 is classically thought of as a cytoplasmic enzyme, although recently it was identified within mitochondrial membranes. This is the case for both mutant SOD1 and to a lesser extent wild type SOD1 [125]. SOD1 ALS transgenic mice have altered mitochondrial morphology and mitochondrial SOD1 accumulation [126,127]. This raises the possibility that mutant SOD1 may drive neurodegeneration by damaging mitochondria.

3.4 Progressive supranuclear palsy and multiple system atrophy

After PD, progressive supranuclear palsy (PSP) is the most common neurodegenerative movement disorder. It presents most frequently in the seventh decade with prominent postural instability and an increasingly hypokinetic syndrome. A classic form of PSP is associated with restricted voluntary eye movements, but the typical "supranuclear" gaze abnormalities are often lacking in a PSP variant called PSP-parkinsonism. A predominantly frontal-subcortical pattern of cognitive decline frequently occurs. Neurodegeneration is seen in the striatum, globus pallidus, subthalamic nucleus, thalamus, basal forebrain, and various brainstem and cerebellar nuclei [128,129].

Tau-containing neurofibrillary tangles are an important histologic feature. The exon 10-containing 4 repeat tau isoform is proportionally elevated in PSP tangles [130]. The microtubule associated protein (MAP) tau gene H1 haplotype is also overrepresented in persons

with PSP and indicates although PSP is a sporadic disease Mendelian factors influence risk [131].

Data consistent with, suggestive of, or indicative of PSP subject mitochondrial perturbation are reported. Brain PET shows frontal lobe hypometabolism [132–135]. Muscle mitochondria have decreased ATP production [136]. Ketoglutarate dehydrogenase and aconitase activities are reduced in the cerebellum [137–139]. Both muscle and brain appear bioenergetically compromised when studied using phospho-magnetic resonance spectroscopy [140]. PSP cybrids in which platelet mitochondria from PSP subjects were transferred to human neuroblastoma cells showed reduced complex I activity and increased free radical production [141,142]. Inhibition of complex I by the toxin annonacin has also been used to model PSP in cultured neurons and rats [143,144] [145]. Mitochondria may therefore play an important role in PSP.

Multiple system atrophy (MSA) is also a hypokinetic movement disorder. Degeneration of striatonigral olivopontocerebellar, and preganglionic autonomic neurons can occur, sometimes in isolation but most often in combination [146]. Reduced brain and skeletal muscle energy metabolism have been shown by in vivo phosphorous MR spectroscopy [147]. Complex I activity was reduced in MSA subject muscle mitochondria [148].

4. Strictly Mendelian neurodegenerative mitochondriopathies

4.1 Huntington's disease

HD is a strictly autosomal dominant, hyperkinetic neurodegenerative movement disorder. Neuropsychiatric symptoms and signs are also prominent. Profound neurodegeneration of the striatal GABAergic medium spiny neurons occurs [149]. It is ultimately caused by a CAG repeat expansion in one copy of the Huntingtin gene on chromosome 4, which encodes a protein called huntingtin [150]. Huntingtin's polyglutamine extension appears to confer a toxic gain-of-property function.

Various metabolism-related enzymes are dysfunctional in HD [151]. Complex I activity is reduced in platelets and muscle from HD subjects [8,152]. Activities of complex II, III, and IV are seen in brain [151]. Toxic inhibition of the ETC enzyme complex II by either 3-nitropropionic acid or malonate induces a pattern of neurodegeneration in mice that is similar to that of human HD [153,154], and these toxins have been extensively used to model HD.

It is currently unclear how mutant huntingtin affects mitochondria [151]. Huntingtin has been shown to physically associate with mitochondrial membranes and interfere with mitochondrial calcium handling [155]. It also interacts with other proteins that may mediate mitochondrial function. Huntingtin has been proposed to interfere with mitochondrial biogenesis by disrupting peroxisome proliferator activated receptor γ coactivator 1 α (PGC-1 α), a transcription co-activator that facilitates mitochondrial biogenesis [156].

4.2 Friedreich's Ataxia

Friedreich's ataxia (FA) is a relatively common autosomal recessive genetic disorder [157]. It presents as progressive sensory loss, weakness, and dyscoordination. Sensory neurons with cell bodies in dorsal root ganglia and which project through the spinal cord dorsal columns degenerate initially, and neurodegeneration later spreads to the spinocerebellar tracts, cerebellar purkinje cells, and corticospinal tracts. Insulin resistance is also a feature. Symptomatic onset most commonly occurs during the second decade.

Causal mutations reside in the FXN gene on chromosome 9 [158]. Often (but not exclusively) mutant alleles contain an expansion of an intronic GAA repeat segment. Point mutations within

exons are occasionally found, and alleles with point mutations are occasionally paired with GAA expansions in individuals with late onset Friedreich's ataxia (LOFA). In rare cases small frameshift or splice site mutations are present and create null alleles. Subjects with null alleles may have an expanded phenotype that includes optic nerve degeneration [159].

FXN encodes frataxin, a mitochondrially targeted protein that is an iron chaperone and plays a role in mitochondrial iron handling [157,160]. Frataxin contributes to iron-sulfur cluster and heme synthesis. Both iron-sulfur clusters and heme are required ETC constituents. Consequences of altered mitochondrial function have been demonstrated in FA subjects [161]. Mitochondrial haplogroup U reportedly associates with a milder phenotype [162].

4.3 Wilson's disease

Persons with Wilson's disease, also called Hepatolenticular Degeneration, may develop neuropsychiatric symptoms and a hypokinetic movement disorder [163]. Profound bulbar dysfunction with dysarthria can be a relatively early sign [164]. The age of onset is variable, but it usually occurs before the sixth decade. Neurodegeneration classically appears as necrosis within the basal ganglia, but can also involve the brainstem, thalamus, cerebellum and cerebral cortex.

Wilson's disease is inherited as an autosomal recessive disorder, with mutations occurring within the ATPase copper transporting beta polypeptide (ATP7B) gene on chromosome 13 [165,166]. The ATP7B protein localizes to mitochondria [167]. Pervasive ETC dysfunction has been demonstrated in liver tissue from Wilson's disease patients [168]. It is postulated recessive mutation of ATP7B leads to perturbed mitochondrial copper homeostasis and, as a consequence, impaired mitochondrial function. Oxidative stress, reduced cytochrome oxidase activity, and activation of intrinsic apoptotic cascades may represent common features of copper-mediated mitochondrial toxicity [169].

4.4 Other Mendelian neurodegenerative mitochondriopathies

The list of diseases in which neurodegeneration occurs and mitochondria are implicated is growing. Neurodegeneration with brain iron accumulation (formerly known as Hallevorden-Spatz disease) and some variants of hereditary spastic paraplegia qualify as neurodegenerative mitochondriopathies, as the responsible mutant proteins localize to mitochondria [35,170]. OPA1, like LHON, is a degenerative optic neuropathy, but unlike LHON it is Mendelian [13]. Charcot-Marie-Tooth (CMT) type 2a, a degenerative disease of the peripheral nerves, is a Mendelian disorder with impaired mitochondrial fusion [171]. CMT type 4a is associated with impaired mitochondrial fission [172,173].

5. Controversies and implications

For the neurodegenerative mitochondriopathies with clear maternal inheritance and known mtDNA mutations, there is general agreement that mitochondria belong at the apex of a neurodegenerative cascade. Working out that cascade has been impeded by a lack of good animal models. Mitochondrial DNA-altered mice have been generated through both selective breeding and transgenic approaches, but the results of these efforts are not disease-specific [174–177]. While functional studies of tissue (often muscle) from affected subjects has contributed to our overall body of knowledge, tissue-derived data is largely descriptive and rarely from brain. Most mechanistic studies have had to rely heavily on cell culture models, and in particular cybrid modeling. Most cybrid cell lines are immortalized, and less reliant on aerobic respiration than primary tissues.

Modeling issues have also influenced research into the predominantly sporadic neurodegenerative mitochondriopathies. It is currently unclear how best to model sporadic

neurodegenerative diseases. To date, this issue has largely been circumvented by using animal models of Mendelian disorders to stand in for their sporadic namesakes. Transgenic mice expressing mutant human APP and SOD1 genes, for example, have dominated AD and ALS research for over a decade. While conceptually unattractive, this practice may come under practical fire if the list of therapeutics that benefit Mendelian disease models but not the actual sporadic diseases they represent continues to grow [41].

Cybrid models have provided potentially valuable insights into the sporadic neurodegenerative mitochondrialopathies, but do not absolutely address the question of how or why mitochondrial dysfunction developed in the individuals that serve as mitochondrial donors. Debates over cybrid data have revolved around whether cybrid mitochondrial dysfunction arises through inherited or somatic mtDNA aberration, arises at all from mtDNA, or even exists. Negative cybrid studies have been reported, but it is reasonable to point out on a technical level negative studies differ substantially from positive studies. Likewise, studies noting maternal inheritance bias in AD and PD, ETC dysfunction in AD and PD brains, ETC dysfunction in AD and PD non-cerebral tissues, and studies of mtDNA mutation and polymorphism have also been questioned [63,72,94,178].

With the strictly Mendelian neurodegenerative mitochondrialopathies, the presence and relevance of mitochondrial function seems well accepted. Where exactly mitochondrial dysfunction sits in the degenerative cascade or how it mediates the degenerative cascade in these disorders is not fully known. To date, much speculation has been given to the role mitochondria play in programmed cell death [179–181].

7. Summary

This review has thematically classified a group of neurodegenerative diseases using mitochondrial dysfunction as a common thread. In addition to manifesting mitochondrial dysfunction, several of these diseases are associated with protein aggregation and were previously grouped along that line. For example, AD is considered an amyloidosis, PD and MSA synucleinopathies, and PSP a tauopathy. It is important to note these are all simply heuristic constructs and not mutually exclusive of each other. It is hoped defining the neurodegenerative mitochondrialopathy group of disorders will help stimulate new insight and new research into what are undeniably a devastating group of disorders.

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Figure 1.

The cybrid technique. The black-filled circles represent nuclei. The ovals represent mitochondria. The circles within the ovals represent mitochondrial DNA, with different patterns indicating mtDNA from different individuals.

Figure 2.
The Alzheimer's disease mitochondrial cascade hypothesis.