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Time to harmonize mitochondrial syndrome nomenclature and classification: A consensus from the North American Mitochondrial Disease Consortium (NAMDC)

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Declaration of Competing Interest

None reported.

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Abstract

Objective: To harmonize terminology in mitochondrial medicine, we propose revised clinical criteria for primary mitochondrial syndromes.

Methods: The North American Mitochondrial Disease Consortium (NAMDC) established a Diagnostic Criteria Committee comprised of members with diverse expertise. It included clinicians, researchers, diagnostic laboratory directors, statisticians, and data managers. The Committee conducted a comprehensive literature review, an evaluation of current clinical practices and diagnostic modalities, surveys, and teleconferences to reach consensus on syndrome definitions for mitochondrial diseases. The criteria were refined after manual application to patients enrolled in the NAMDC Registry.

Results: By building upon published diagnostic criteria and integrating recent advances, NAMDC has generated updated consensus criteria for the clinical definition of classical mitochondrial syndromes.

Conclusions: Mitochondrial diseases are clinically, biochemically, and genetically heterogeneous and therefore challenging to classify and diagnose. To harmonize terminology, we propose revised criteria for the clinical definition of mitochondrial disorders. These criteria are expected to standardize the diagnosis and categorization of mitochondrial diseases, which will facilitate future natural history studies and clinical trials.

Keywords

Mitochondrial disease; Mitochondrial disorders; Oxidative-phosphorylation; Mitochondrial DNA

1. Introduction

Primary mitochondrial disorders are a group of clinically and genetically diverse conditions caused by defects in the metabolic pathways in mitochondria [1]. The pathogenesis

of primary mitochondrial disorders is due to mutations in more than 350 genes, both nuclear and mitochondrial. It is often difficult - even for expert clinicians - to diagnose mitochondrial diseases (MtDs) because of their rarity; clinical, biochemical, and genetic heterogeneity; their phenotypic overlap with other disorders; and their lack of specific biomarkers[2]. As a consequence, patients are frequently misdiagnosed and consult, on average, more than eight physicians during their “diagnostic odyssey” [3].

Although individual MtDs are very rare, in toto, they are relatively frequent: the estimated prevalence of childhood-onset MtDs ranges from 5 to 15 cases per 100,000 individuals, and the prevalence of adult-onset forms has been estimated to be 9.6 cases per 100,000 individuals for mitochondrial DNA (mtDNA) related disorders and 2.9 cases per 100,000 individuals for nuclear DNA (nDNA) related disorders [4,5]. These disorders are often progressive and cause high morbidity and mortality among both pediatric and adult populations [6].

Specific clinical features can be suggestive of MtDs, especially when grouped in particular combinations that define recurrent and recognizable syndromes, which we refer to as classical mitochondrial syndromes (e.g., Leigh syndrome, Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS), or Myoclonic Epilepsy with Ragged-Red Fibers (MERRF). However, many mitochondrial disorders manifest phenotypes that do not conform to a classical mitochondrial syndrome. In addition to clinical characterization, definitive diagnosis is often achieved through histological, biochemical, and genetic testing.

To provide a tool to integrate clinical, biochemical, laboratory, and genetic findings, diagnostic criteria for adult with suspected mitochondrial disorders were published in 1996 (Adult Criteria, AC) [7], and modified for a pediatric population in 2002 (Modified Adult Criteria, MAC) [8]. A second scoring system for pediatric patients was presented in 2002 (Mitochondrial Disease Criteria, MDC), [9] and subsequently validated in 2006 [10]. These criteria have been demonstrated to retain utility in guiding the diagnosis of MtD [11].

In the 16 years since the last publication on MtD diagnostic criteria, there has been an outburst of new phenotypic and genotypic information about these disorders. New technologies in genetic and functional testing further require integration into the diagnostic criteria. These new data have facilitated the diagnosis and classification of these complex diseases in many patients. Investigators in the North American Mitochondrial Disease Consortium (NAMDC) recognized a need to revise the diagnostic criteria for mitochondrial disorders to incorporate this new information and to attain greater consistency and rigor in diagnostic criteria and terminology.

NAMDC assembled a committee of experts in the diagnosis of mitochondrial disorders to update the diagnostic criteria and achieve standardized definitions of clinical manifestations, laboratory abnormalities, and diagnoses. The primary goals were to standardize the clinical classification of MtDs. The development of research diagnostic criteria is not merely an academic exercise, but rather a critical step towards improving reproducibility in clinical research.

2. Materials and methods

The NAMDC Diagnostic Criteria Committee was composed of 11 members with diverse biomedical expertise including: pediatric and adult neurologists, clinical geneticists, clinical biochemical geneticists, and academic diagnostic laboratory directors. They reviewed relevant literature and sought to develop consensus recommendations. Their first iteration of the diagnostic criteria was completed in March 2012. This work built upon the original set of diagnostic criteria for adults (AC) published in 1996 by Walker et al. [7] and subsequent modifications by Bernier et al. [8] (MAC) as well as Wolf et al. (MDC) in 2002 [9] to include the pediatric population. Specifically, we have incorporated advances in diagnostic modalities to bring the criteria up-to-date with current knowledge. After the first draft was completed, the revised criteria were applied to MtD subjects enrolled with complete data in the NAMDC Registry. Since 2011, NAMDC has maintained this Registry, which has extensive clinical, biochemical, histological, and molecular genetic data on over 1300 patients with MtDs [12]. De-identified data extracted from the eCRFs of the 50 random patients were evaluated. Results of this analysis were then used to improve the criteria. Additional revisions to the criteria were discussed via email and teleconferences among the members of the Committee. The criteria were then applied to all subjects enrolled in the NAMDC Registry. The results from this process and subsequent modifications were used by the Committee to generate a second iteration of the Criteria. These were unanimously approved by the 11 members of the working group and the NAMDC site investigators, and finalized in Alexandria, VA, on June 25, 2019 during the NAMDC face-to-face meeting at the United Mitochondrial Disease Foundation (UMDF) 2019 Symposium.

3. Results

3.1. Important advances in the clinical classification of mitochondrial diseases

3.1.1. Recognition of multisystem disease—One of the major challenges for the diagnosis of MtDs is the clinical heterogeneity of these disorders. Most of the patients enrolled in the NAMDC Registry have multi-systemic disorders (≥3 affected organs), characteristically affecting tissues with high-energy demands, such as central nervous system, skeletal muscle, eye, and heart [13]. Their phenotypes often do not conform to widely recognized “classical” mitochondrial syndromes (20.1%) [12]. Moreover, many patients with MtDs report an average of 16 symptoms [14]. The NAMDC Diagnostic Criteria therefore recognize multisystem disease as a frequent mitochondrial clinical presentation.

3.1.2. Harmonization of classical clinical mitochondrial syndrome definitions —While many patients enrolled in the NAMDC Registry with MtDs were assigned to well-known classical syndromes due to the presence of cardinal signs or symptoms, these syndromes have lacked uniform definitions. In reviewing patient data entered into the NAMDC Registry, we have observed that these syndromes are frequently misdiagnosed, often based on the incorrect assumption that a specific genetic mutation always corresponds to a specific phenotype. This was the case, for example, with MELAS syndrome, diagnosed in 119 patients enrolled in the Registry before the definition of the diagnostic criteria, and

confirmed only in 60 patients after their application [12]. Thus, we have specified criteria for syndromes based upon their original descriptions and subsequent reports that refined their distinctive features. Application of these criteria for classical mitochondrial syndromes is necessary to better define the clinical phenotype. The classical mitochondrial syndromes and defining criteria are enumerated in Table 1.

3.1.3. Revising phenotypes of established clinical syndromes—One example of how the diagnostic criteria were refined is illustrated by the Chronic Progressive External Ophthalmoplegia (CPEO) and CPEO-plus syndromes. When the first set of criteria was applied to the NAMDC patients' Registry, the diagnosis of "CPEO" required the presence of isolated ptosis, ophthalmoparesis, or both. Any additional clinical manifestations would have led to the assignment of a patient to the "CPEO-plus" category. However, in the stage one analysis of 878 NAMDC Registry patients, we observed that only one out of 28 individuals identified as CPEO fulfilled criteria for the diagnosis of isolated CPEO, while the other 27 patients with ptosis and/or ophthalmoparesis also had evidence of a more generalized myopathy with limb weakness, exercise intolerance, and/or dysphagia. Based upon these data and a review of the literature [15–18], we revised the definition of CPEO to include limb-myopathy, exercise intolerance, and dysphagia. Involvement of any other organ or system (e.g., non-skeletal muscle) would lead to the syndromic designation of "CPEO-plus", unless the patient's manifestations fulfilled criteria for Kearns-Sayre syndrome (KSS), Mitochondrial NeuroGastroIntestinal Encephalomyopathy (MNGIE), or other classical mitochondrial syndrome.With these criteria, we are able to differentiate the pure myopathic syndrome (CPEO) from multisystem disorders (CPEO-plus, KSS, and MNGIE). Longitudinal studies are necessary in order to assess the frequency of developing multisystem disease in patients with CPEO.

3.1.4. Updating diagnostic criteria to reflect current clinical practice—The often-cited historical criteria for KSS are an obligate triad of: CPEO, pigmentary retinopathy, and onset before age 20 years plus one of the following three manifestations: cardiac conduction block, ataxia, or elevated cerebrospinal fluid (CSF) protein greater than 100 mg/dL. We noted shortcomings with this definition including: the requirement of age-of-onset before 20 years, which is an arbitrary cut-off not well-supported by data, and the measurement of CSF protein levels, which are rarely obtained in current clinical practice for suspected KSS patients. Hence, we decided not to include these as criteria for the diagnosis of KSS. Accordingly, we replaced the original definition of KSS with the tetrad of: 1) ptosis and/or progressive external ophthalmoplegia, 2) pigmentary retinopathy, 3) cardiac conduction block, and 4) skeletal muscle involvement.

Myoclonic Epilepsy with Ragged-Red Fibers (MERRF) is a multisystem disorder clinically characterized by myoclonus, epilepsy, ataxia, and weakness [19]. The presence of ragged-red fibers (RRFs) in skeletal muscle biopsies has been a "classical" feature of the syndrome. Based on the observation that muscle biopsies have been performed less frequently after the introduction of next generation sequencing (NGS) techniques (whole mtDNA sequencing, gene panels, whole exome and genome sequencing) and that, occasionally, RRFs may not be observed in patients with MERRF [20] we now exclude the presence of RRFs

from the clinical definition of the syndrome. Recently, Finsterer and colleagues used a standardized approach to clarify the definition of MERRF [21]. They based their definition on clinical manifestations, and did not include the presence of RRFs. In their study, the distinctive feature of this rare mitochondrial disorder was not surprisingly myoclonic epilepsy. Interestingly, they have also assessed the strength of gene-disease associations and have confirmed that MERRF is primarily an MT-TK disease, with pathogenic variants in this gene accounting for ~90% of MERRF patients, similar to the NAMDC cohort [12].

The syndrome originally described as “benign infantile mitochondrial myopathy due to reversible cytochrome *c* oxidase (COX) deficiency” also required re-assessment [22]. This syndrome was originally defined by early onset diffuse skeletal muscle weakness with COX-deficiency, hypotonia, and respiratory insufficiency that spontaneously improves by 3 years of age. However, this syndrome should be described as reversible infantile myopathy with respiratory chain deficiency because defects in multiple respiratory chain complexes in addition to COX have been reported [23,24].

Through these revisions, we have endeavored to generate the necessary strict well-delineated standardized criteria for accurate diagnoses of these syndromes.

3.1.5. Recognition of new clinical syndromes—Although the original development of the classification of MtD syndromes has greatly facilitated the recognition and diagnosis as well as classification of this heterogeneous group of disorders, the majority of patients, as illustrated in the cohort of patients in the NAMDC Registry, do not fulfill the criteria for a “classical” clinical syndrome [12]. Novel clinical syndromes continue to be reported in association with mitochondrial dysfunction, and at an increasing rate in the last decade due to the wider use of next-generation DNA sequencing techniques. To begin to address the conundrum of categorizing this large group of patients, we have tabulated the new clinical syndromes as well as organ/system manifestations strongly suggestive of mitochondrial disorders in Tables 2 and 3. Eventually, these and other well-defined and specific clinical phenotypes may be included with the “classical” syndromes, after a thorough analysis of defining criteria.

3.2. Beyond clinical classification: The importance of diagnostic studies (biochemistry, genetics, histology, metabolic profile, and neuroimaging)

The diagnostic evaluation of patients with a mitochondrial disorder typically begins with the identification of the clinical features that can either be part of a well-defined mitochondrial syndrome or involve organs in specific patterns that suggest MtDs. Although recognition of hallmark manifestions of MtDs is critical to initiate the diagnostic process, clinical features alone are often insufficient to make a definite diagnosis of MtD. Data from the following five laboratory analyses are usually necessary to definitively diagnose MtDs: biochemistry, histology (skeletal muscle, liver, and heart), metabolic markers, neuroimaging, and molecular genetic defects (nuclear or mitochondrial).

3.2.1. Biochemistry—Prior to the identification of causative genetic mutations, mitochondrial diseases were typically recognized by detection of defects in mitochondrial oxidative phosphorylation enzymes. Robust quality standards must be met when considering

biochemical data, including specimen collection, handling, and shipment. [25] Most commonly collected tissues include skeletal muscle, liver, heart, brain, cultured fibroblasts, and peripheral white blood cells. A normal protein/activity marker (e.g., citrate synthase) has to be concomitantly measured in order to avoid the occurrence of false positive results.

3.2.2. Histology—Biopsy of an affected tissue in patients with suspected MtDs often provides important diagnostic information on the structure and function of mitochondria. Systematic analysis of frozen skeletal muscle sections is an important diagnostic tool for evaluating MtDs. The use of modified Gomori trichrome, succinate dehydrogenase (SDH), cytochrome *c* oxidase (COX), and SDH/COX combined staining often reveal mitochondrial defects, such as COX deficiency or mitochondrial proliferation evident as ragged-red fibers (RRFs) or ragged-blue fibers (RBFs), [26] Although not entirely specific, these findings have been considered classical features of MtD pathology. [27]

3.2.3. Metabolic profile—Accumulations of metabolites caused by mitochondrial dysfunction such as lactate, pyruvate, and intermediates of the Krebs cycle have been used as a diagnostic clue in the clinical investigation of MtDs. A persistent elevation of plasma lactate, elevated CFS lactate, and serum lactate/pyruvate ratio > 20 are considered highly suspicion of MtDs. Moreover, elevated urine 3-methylglutaconic acid at least twice above normal reference range is strongly associated with specific MtDs (e.g. Barth's syndrome and TMEM70 defects). [28]

Nevertheless, those alterations often lack both specificity and sensitivity to definitively diagnose mitochondrial disorders, and can be found in conditions causing secondary mitochondrial dysfunction. [29–31] Recently, serum fibroblast growth factor-21 (FGF-21) and serum growth and differentiation factor-15 (GDF-15) have emerged as novel, potential biomarkers of MtDs, particularly mitochondrial myopathies. [32,33] Both markers may be more sensitive and specific than currently used metabolites [34]; however, elevations of FGF-21 and GDF-15 have been observed with a range of non-mitochondrial disorders (e.g., obesity, diabetes, and liver disease) [35–37] and need to be better validated.

3.2.4. Neuroimaging—Diagnostic utility of brain imaging with Magnetic Resonance Imaging (MRI) as well as detection of tissue metabolites using Magnetic Resonance Spectroscopy (MRS) have been well-documented in mitochondrial disorders. [38–41] Common structural findings include bilateral increased T2- and FLAIR-signals in the deep gray matter, stroke-like lesions in non-large vessel territories, leukoencephalopathy, and cerebral and cerebellar atrophy. [39] MRS with ^{31}P and ^{1}H spectra is commonly used to evaluate MtDs, and allows for the identification of lactate, choline, *N*-acetylaspartate, and phosphorus metabolites.

3.2.5. Molecular genetics—Since the initial identification of the first mtDNA mutations in 1988, [42–44] detection of pathogenic molecular genetic variants has become the gold standard for diagnosis of MtDs. The most recent American College of Medical Genetics and Genomics (ACMG) guidelines [45] must be followed for the interpretation of nuclear genome sequence variants. Regarding mtDNA point mutations, not only the position of the variants and the nucleotide change must be considered, but also the

heteroplasmic levels. Rapid advances in molecular genetic testing and clinical availability of Next Generation Sequencing (NGS) techniques have enhanced the diagnostic ability of clinicians. [46–48] For example, it is now possible to detect single-deletion by NGS or long-range polymerase chain reaction (PCR) in urine, blood, or buccal swab of patients. [49,50]

4. Conclusions

The identification and recognition of clinical phenotypes are typically the first steps to achieve specific diagnoses of mitochondrial patients and to focus confirmatory genetic testing. Advances in the field of mitochondrial medicine have driven the need to revise the definition of MtDs, to improve patient diagnosis and classification as well as clinical trial readiness through natural history studies.

The issue of clinical syndromic phenotypes has been addressed by this paper, with delineation of specific criteria for classic mitochondrial syndromes. We have based our criteria on review of the literature, expert opinion, and real-world data present in our NAMDC registry, followed by rigorous analysis and revisions by the members of the Committee.

We recognized limitations of the proposed approach, including analyses of retrospective data and potential biases of existing clinical classification systems. Prospective use of these syndromic definitions will be necessary for validation and further refinement. We plan to optimize the diagnosis of mitochondrial disorders by implementing an automated algorithm into the NAMDC Registry that will assign a diagnosis in real time, based on pre-programmed clinical criteria fulfilling the NAMDC criteria. Moreover, a data-driven machine-learning approach may be applied not only to refine diagnostic guidelines for assigning patients to current diagnostic entities, but potentially more interestingly to identify novel phenotypic presentations among the currently clinically unclassified mitochondrial patients.

It will be necessary to periodically review definitions of the syndromes according to the advances in our knowledge. It is important to emphasize that the current criteria are not intended for clinical diagnoses, but rather meant to be used for classification of patients in research studies. Nevertheless, we have noted the importance of clinical laboratory tools to diagnose MtDs. It is also critical to bear in mind that mitochondrial disease typically evolve over years before reaching the full classical syndrome, as some symptoms naturally precede others. Although all the signs/symptoms are necessary to classify a patient within a specific syndrome, this classification should not delay patients' diagnosis and treatment.

Further research is needed to better understand this important group of diseases and develop new therapeutic strategies. Although MtDs taken together are frequent, [51] the incidence of each individual disorder is rare. As with other rare disorders, the small numbers of patient, complex and often delayed diagnoses, clinical heterogeneity, and geographic dispersion, represent additional challenges to the development of clinical trials and subsequent evidence-based clinical care approaches. We believe that the proposed

clinical NAMDC criteria will contribute to streamlining nomenclature and diagnoses across centers. This will, in turn, help collaborations within the US and internationally to simplify translational research efforts with the ultimate goal to facilitate clinical development of promising novel therapies.

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Abbreviations:

MtD	Mitochondrial disease
mtDNA	mitochondrial DNA
MELAS	Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes
MERRF	Myoclonic Epilepsy with Ragged-Red Fibers
CPEO	Chronic Progressive External Ophthalmoplegia
KSS	Kearns-Sayre syndrome
MNGIE	Mitochondrial NeuroGastroIntestinal Encephalomyopathy
NAMDC	North American Mitochondrial Disease Consortium
MAC	Modified Adult Criteria
MDC	Mitochondrial Disease Criteria
AC	Adult Criteria
COX	cyto-chrome *c* oxidase
NGS	next generation sequencing
RRFs	ragged-red fibers
SDH	succinate dehydrogenase
RBFs	ragged-blue fibers

FGF-21	fibroblast growth factor-21
GFDF-15	growth and differentiation factor-15
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
ACMG	American College of Medical Genetics and Genomics

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Table 1

Classical mitochondrial syndromes.

Alpers syndrome
All of A – C:
A. Psychomotor regression
B. Intractable seizures (confirmed by EEG and lack of response to at least two anti-seizure medications)
C. Hepatopathy (Liver disease/dysfunction)
Aminoglycoside-induced deafness
A. Sensorineural hearing loss in association with aminoglycoside exposure
Barth syndrome
Both A and B, plus at least one of C – E:
A. Male gender
B. Dilated cardiomyopathy or non-compaction cardiomyopathy, defined by echocardiogram or MRI
C. Neutropenia
D. At least one of 1–2:
1. Growth delay
2. Prolonged pubertal growth spurt
E. At least one of 1–3:
1. Hypotonia
2. Skeletal muscle weakness
3. Chronic fatigue
Chronic Progressive External Ophthalmoplegia (CPEO)
A. Ptosis, Progressive External Ophthalmoplegia (PEO) or both (limb myopathy, exercise intolerance, and dysphagia may also be present)
CPEO-plus
Both A and B:
A. Ptosis, Progressive External Ophthalmoplegia (PEO) or both (limb myopathy, exercise intolerance, and dysphagia may also be present)
B. Any other manifestation listed in Table 2 but not fulfilling criteria for KSS, MNGIE, or SANDO
Kearns-Sayre syndrome (KSS)
All of A – D:
A. Ptosis, Progressive External Ophthalmoplegia (PEO) or both
B. Pigmentary retinopathy
C. Cardiac conduction block

D. Skeletal muscle involvement (see Table 2)

Leber hereditary optic neuropathy (LHON)

Both A and B:

A. Acute-onset central vision loss in one or both eyes

B. Family history compatible with maternal inheritance and not autosomal dominant inheritance (e.g., no male-to-male transmission)

Leigh syndrome

Both A and B:

A. Neurodevelopmental regression or delay

B. Bilateral lesions of the basal ganglia, midline brainstem or both by brain CT, brain MRI (T2/FLAIR hyperintense lesions)

Mitochondrial Encephalomyopathy, Lactic Acidosis and Stroke-like episodes (MELAS)

Both A and B:

A. Stroke-like episodes (sudden-onset focal neurological deficit with brain MRI or CT showing a cerebral lesion that does not conform to a large vessel territory and typically affects cortex and adjacent white matter)

B. Encephalomyopathy (see Table 3)

Mitochondrial NeuroGastroIntestinal Encephalomyopathy (MNGIE)

All of A – E:

A. Ptosis, Progressive External Ophthalmoplegia (PEO) or both

B. Gastrointestinal dysmotility (see Table 2)

C. Neuropathy

D. Cachexia

E. Diffuse or patchy white matter lesions evident on brain MRI

Myoclonic Epilepsy with Ragged-Red Fibers (MERRF)

All of A – C:

A. Myoclonic seizures or myoclonus plus seizures

B. Ataxia

C. Mitochondrial myopathy (see Table 2)

Neuropathy Ataxia and Retinitis Pigmentosa (NARP)

All of A – C:

A. Peripheral neuropathy

B. Ataxia

C. Pigmentary retinopathy

Pearson syndrome

Both A and B:

A. Sideroblastic anemia

B. Exocrine pancreatic dysfunction

Reversible infantile myopathy with respiratory chain enzyme deficiencies

All of A – D:

A. Diffuse myopathic weakness

B. Hypotonia

C. Respiratory insufficiency (chronic shortness of breath)

D. Spontaneous improvement by age 3 years

Sensory Ataxic Neuropathy Dysarthria Ophthalmoplegia (SANDO)

All of A – D:

A. Sensory ataxia

B. Neuropathy

C. Dysarthria

D. Ophthalmoparesis

Table 2

Clinical manifestations of mitochondrial disease by organ system

Neurological

- Ataxia: cerebellar*
- Ataxia: sensory*
- Chorea*
- Dementia*
- Dystonia
- Headaches (non-migraine)
- Hyperreactive reflexes (incl. Babinski sign, Hoffman sign)
- Hypotonia
- Migraine headaches
- Myoclonus
- Neuropathy:axonal
- Neuropathy: demyelinating
- Ophthalmoparesis
- Parkinsonism*
- Seizures*
- Spasticity
- Strokes or Stroke-like lesions*
- Encephalopathy (at least one neurological manifestation marked with an *)

Psychiatric

- Generalized anxiety disorder°
- Depressive Disorder Due to Another Medical Condition°
- Psychotic disorder due to a another medical condition°

Developmental

- Fine motor disability
- Gross motor disability
- Language disability
- Delayed social development
- Cognitive delay or regression
- Abnormal neuropsychological test (not including only behavioral abnormalities)
- Growth delay
- Prolonged pubertal growth spurt
- Psychomotor regression (loss of acquired skills)
- Congenital Hypotonia (floppy baby)
- Autism spectrum disorder°
- Intellectual disability

Muscular

- Dysarthria
- Dysphagia
- Exercise intolerance
- Weakness
- Myoglobinuria/Rhabdomyolysis
- Myopathy
- External ophthalmoparesis
- Ptosis

Cardiac

- Cardiac conduction block
- Dilated cardiomyopathy
- Arrhythmia
- Cardiomyopathy (Hypertrophic, Non-compaction, Restrictive)
- Wolff-Parkinson-White

Renal

- Renal tubular acidosis (e.g. Fanconi syndrome)
- Nephrotic syndrome
- Focal segmental glomerulosclerosis
- Other renal

Hepatic

- Hepatopathy (e.g. steatosis, oncocytic changes by liver biopsy)
- Cirrhosis
- Hepatic failure (e.g. hepatic encephalopathy)

Endocrine

- Diabetes mellitus
- Hypothyroidism
- Hypogonadotropic hypogonadism
- Hypoparathyroidism
- Adrenal insufficiency
- Other endocrine

Hematologic

- Sideroblastic anemia
- pancytopenia

Otologic

- Sensorineural hearing loss

Ophthalmologic#

- Cataracts
- Optic neuropathy
- Pigmentary retinopathy

Constitutional

- Cachexia/Thinness (BMI < 18.5)
- Chronic fatigue
- Chronic shortness of breath
- Short stature (patient's height is below the 3rd percentile)
- Exercise intolerance

Gastrointestinal

• Recurrent nausea/vomiting	• *Intestinal dysmotility
• *Dysphagia	• Gastrointestinal dysmotility (at least one gastrointestinal manifestation marked with an *)
• *Gastroparesis	
• *Gastrointestinal pseudo-obstruction	• Exocrine pancreatic dysfunction
Miscellaneous	
• Multiple symmetric lipomatosis	• Idiopathic osteopenia/pathologic fractures

° defined according to DSM-5; Black, Donald W., and Jon E. Grant. DSM-5® Guidebook: The Essential Companion to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, American Psychiatric Publishing, 2014.

External ophthalmoparesis under “muscular” and “neurological”; ptosis under “muscular”.

Table 3

Criteria for mitochondrial clinical syndromes.

Cardiomyopathy
At least one of A – D:
A. Dilated cardiac muscle abnormality defined by echocardiogram or MRI
B. Hypertrophic cardiac muscle abnormality defined by echocardiogram or MRI
C. Restrictive cardiac muscle abnormality defined by echocardiogram or MRI
D. Left ventricular non-compaction defined by echocardiogram or MRI
Diabetes and deafness (DAD)
Both A and B:
A. Diabetes mellitus
B. Sensorineural hearing loss
Encephalomyopathy
All of A – C:
A. Clinical manifestation in skeletal muscle (see Table 2)
B. Encephalopathy (see Table 2)
C. Does not fulfill criteria for any other mitochondrial syndrome
Hepatocerebral syndrome
All of A-C
A. Progressive or persistent liver dysfunction
B. Encephalopathy (see Table 2)
C. Absence of confirmed Alpers-Huttenlocher syndrome Leukoencephalopathy
At least one of A – C, plus D:
A. Cognitive impairment
B. Increased skeletal muscle tone (spasticity)
C. Hyperactive reflexes
D. Diffuse, patchy, or cystic white matter lesions evident on brain MRI
Maternally inherited deafness
Both A and B:
A. Sensorineural hearing loss
B. Maternally inherited hearing loss
Multi-systemic syndrome
Both A and B:
A. Clinical manifestations must include at least three of the organ system presentations (including neurologic, developmental, muscular, cardiac, renal, hepatic, endocrine, hematologic, otologic, ophthalmologic, and gastrointenstinal- see Table 2).
B. A progressive clinical course with episodes of exacerbation (e.g. following intercurrent illnesses).

Cardiomyopathy