
IN THE
NAME OF GOD

THE FLOPPY INFANTS METABOLIC PERSPECTIVE

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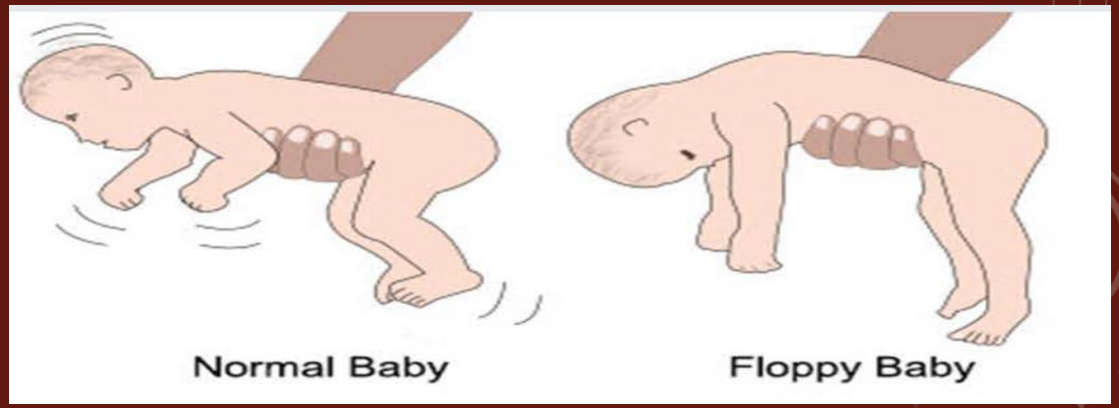
INTRODUCTION

- Hypotonia is defined as decreased resistance to passive movement and is a common abnormal clinical finding in infants
- The maintenance of muscle tone depends on the integrity and proper function of the nervous system is either at the level of the motor cortex, ascending and descending tracts, peripheral nerves, the motor endplate and muscle.
- A change in any of these areas can be manifested in a box of hypotonic syndrome.
- The incidence of congenital hypotonia

  in term infants to be 0.8/1000 births



- The commonest cause is hypoxic ischemic encephalopathy,

Neurology 10.8 (2018): 720-726.

Clinical Genetics. 2021;1–6.

Classification

- There are two approaches for classification.
- I) The first is based on identifying the neuro-anatomical site of the lesion or insult.
- Careful neurological examination localise the site of the lesion to the upper motor neuron (UMN) or lower motor neuron (LMN) unit.
- II) The second is to determine whether or not the hypotonia is accompanied by weakness
- Weakness is reduced strength in one or more muscles.
- Weakness is uncommon in UMN hypotonia except in the acute stages.
- Hypotonia with profound weakness therefore suggests involvement of the LMN.

Neurology 10.8 (2018): 720-726.

Classification

- Hypotonia is divided into two groups:
- 1) Primary hypotonia (paralytic group) : related to the involvement of structures composing the motor unit (anterior horn cell, nerve roots, peripheral nerves, and muscles)
- 2) Secondary hypotonia (nonparalytic group) : resulting from CNS injuries, genetic disorders, systemic diseases, or conditions affecting tendons and ligaments
- Central causes, which account for 60%-88% of the cases of hypotonia, and the less frequent peripheral causes, which account for 15%-30% of the causes of hypotonia, and as a whole, represent neuromuscular diseases

Neurology 10.8 (2018): 720-726.

INDICATORS OF CENTRAL HYPOTONIA

- Social and cognitive impairment, in addition to motor delay
- Dysmorphic features implying a syndrome or other organ malformations sometimes implying a syndrome
- Fisting of hands;
- Normal or brisk tendon reflexes
- No evidence of muscle fasciculations
- Muscle power is relatively preserved and axial weakness is a significant clinical feature
- Crossed adductor response or scissoring present upon vertical suspension;
- Seizures;
- History that is suggestive of hypoxic-ischemic encephalopathy, birth trauma or symptomatic hypoglycaemia
- Postural reflexes are generally preserved in infants with cerebral hypotonia despite a paucity of spontaneous movements

Pediatr Neurosci. 2016 Jan-Mar; 11(1): 2–6.

. Cureus 2020 12(2): e6922.

INDICATORS OF PERIPHERAL HYPOTONIA

- Delay in motor milestones with relative normality of social and cognitive impairment
- Family history of neuromuscular disorders/maternal myotonia
- Reduced or absent deep tendon jerks and increased range of joint mobility
- There is weakness in the antigravity limb muscles
- They can have deformities of bones or joints (arthrogryposis).
- Frog-leg posture or ‘jug handle’ posture of
- Myopathic facies (open mouth with tented upper lip, poor lip seal when sucking, lack of facial expression, ptosis and restricted ocular movements)
- Postural reflexes are absent or diminished, and limbs that lack voluntary movement
- Babies with anterior horn cell disease usually have sparing of extra-ocular muscles while the disorders of neuromuscular junctions may have ptosis and extra-ocular muscle weakness
- Fasciculations, often observed in the tongue

Pediatr Neurosci. 2016 Jan-Mar; 11(1): 2–6.

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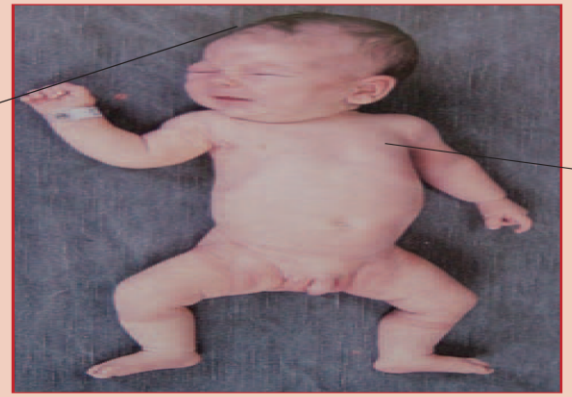
CLINICAL CLUES ON NEUROLOGICAL EXAMINATION



Floppy strong

Increased tendon reflexes
Extensor plantar response
Sustained ankle clonus
Global developmental delay
Microcephaly or suboptimal head growth
Obtundation convulsions
Axial weakness a significant feature

Floppy weak

Hypo- to areflexia
Selective motor delay
Normal head circumference and growth
Preserved social interaction
Weakness of antigravitational limb muscles
Low pitched weak cry
Tongue fasciculations
Paradoxical chest wall movement

Upper motor neuron disorder
Central hypotonia

Lower motor neuron disorder
Peripheral hypotonia

Genetic studies
Karotyping
FISH methylation studies
VLCFA

Triosomy 21
Prader-Willi syndrome
Zellweger syndrome

CT/MRI

Hypoxic ischaemic encephalopathy
Cerabral malformations

Creatine kinase assay
EMG
Nerve conduction studies

DNA-based mutation analysis if available

Spinal muscuar dystrophy
Congenital myotonic dystrophy
Congenital muscular dystrophies

Muscle or nerve biopsy

Congenital structural myopathies

IMPORTANT DIAGNOSTIC CLUES ON EXAMINATION

Practice Pearls:

* Abnormalities of respiratory rate, pattern, or diaphragmatic movement and congenital myopathies.

* Cardiomyopathy and carnitine deficiency Consider, fatty acid oxidation disorders, acid maltase deficiency, Pompe's disease.

* Hepatosplenomegaly and storage disorders or TORCH.

* Renal cysts, liver dysfunctions, high forehead and wide fontanelles e Zellweger's spectrum disorder.

* Congenital cataracts, glaucoma and oculocerebrorenal (Lowe) syndrome.

* Hypopigmentation, undescended testes and Prader Willi syndrome.

* Abnormal fad pad and nipples inverted in CDG.

* Retinitis pigmentosa is seen in in Neonatal adrenoleukodystrophy

* Examination of the mother

  - Congenital myotonic dystrophy
  - Myasthenia gravis

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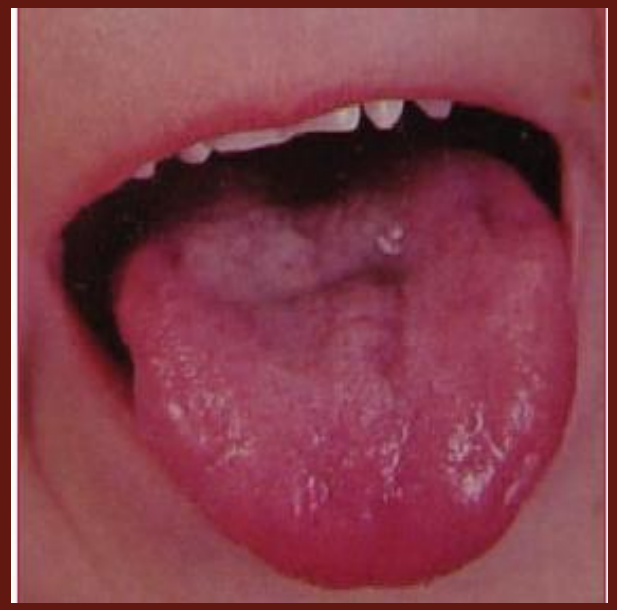
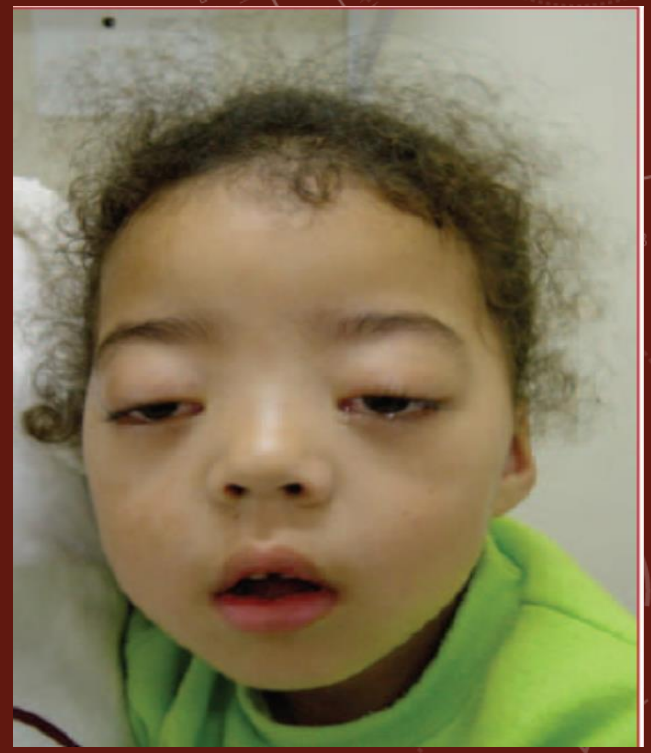
PHYSICAL EXAMINATION



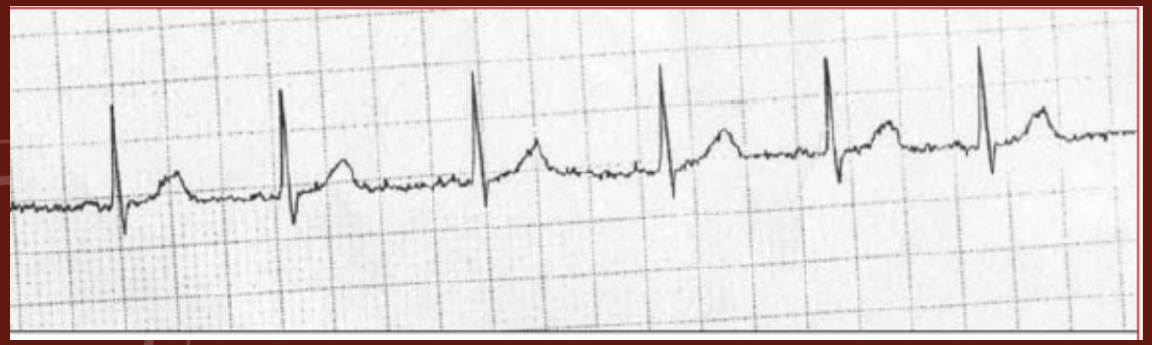
Examine the tongue for size and fasciculations.
Fasciculations, irregular twitching movements, generally indicate an abnormality of the anterior horn cells

Enlargement of
the tongue may suggest a storage disorder such as Pompe's disease



Ptosis and external ophthalmoplegia in a floppy weak child suggestive of myasthenia gravis

ECG of a floppy infant with spinal muscular atrophy



BENIGN CONGENITAL HYPOTONIA

- It is a nonprogressive neuromuscular disorder present at birth that delays neuropsychomotor development milestones.
- It is characterized by symmetrical muscle flaccidity with normal DTR .
- The term ‘benign essential hypotonia’ or ‘hypotonia with favourable outcome’ should be used with caution since newer investigative techniques have resulted in most previously labelled cases being classified into specific disorders.
- Patients labelled as ‘hypotonia with favourable outcome’ should fulfil all of the following criteria:
- 1• early hypotonia, usually since birth
- 2• active movements of limbs and normal tendon reflexes
- 3• normal or mild motor retardation that improves later on
- 4• normal muscle enzymes, EMG, motor nerve conduction studies (MNCS) and histology.
- 5• It is a diagnosis of exclusion.

Residência Pediátrica 2018;8(supl 1):39-43

INVESTIGATIONS

- The first step is to determine the area condition, either brain, spinal or motor unit.
- The brain and peripheral nerves are damaged in some diseases of lipid and mitochondrial disorders.
- Brain and skeletal muscle are abnormal in acid maltase deficiency and neonatal myotonic dystrophy.
- Small with HIE hypoxic damage may have spinal cord.
- Disorders of the motor unit causes severe hypotonia at birth condition in breathing and cause perinatal asphyxia

Neurology 10.8 (2018): 720-726.

INVESTIGATIONS FOR CENTRAL CAUSE

- For infants with central hypotonia, initial investigations include karyotype and neuroimaging (CT or MRI scan).
- Cranial MRI will identify patients with structural CNS malformations, neuronal migration defects and those with white matter changes (congenital muscular dystrophies in particular).
- A karyotype is a must in the dysmorphic hypotonic child. This can be combined with FISH testing if Prader-Willi syndrome is suspected.
- An excessive range of joint mobility, unusual joint postures, the ability to do various contortions of the limbs and/or hyperelasticity of the skin are important diagnostic clues.
- Hypotonia may also be prominent in connective tissue diseases such as Ehlers Danlos or Marfan's syndrome.

Neurology 10.8 (2018): 720-726.

INVESTIGATIONS OF CENTRAL HYPOTONIA

- Serum electrolytes, calcium and phosphate Including, serum alkaline phosphatase, venous blood gas, thyroid function tests
- Plasma copper/caeruloplasmin assay (as screening test for Menkes syndrome)
- Chromosomal analysis (trisomy), DNA methylation studies or FISH for Prader-Willi syndrome
- Plasma amino acids , AC, and organic acids urine
- Urine mucopolysaccharide screen (GAG)
- Molecular/biochemical diagnosis of pro-collagen disorders
- Very long chain fatty acids and 7 dehydrocholesterol
- Isoelectric focusing of the sialotransferine, N- and O- glycan analysis
- Ophthalmology review
- Genetic testing (WES)

Italian Journal of Pediatrics (2016) 42:78

Neurology 10.8 (2018): 720-726.

INVESTIGATIONS OF PERIPHERAL HYPOTONIA

- Creatinine Kinase. Aldolase , and LFT

  An increased CK, aldolase, ALT and AST are usually indicative of a dystrophic process
- Lactate. Pyruvate
- EMG/NCS/repetitive nerve stimulation test.
- Muscle biopsy (histology, immunohistochemistry, electron microscopy, respiratory chain enzyme analysis).
- Genetic testing : could be recognized most different types of congenital myopathy, myotonia and dystrophies
- SMN gene test by PCR detects 95% of cases of spinal muscular atrophy type 1.

  DNA Xp21 deletion testing (PCR assays) can confirm the diagnosis in 65% of males

  with Duchenne muscular dystrophy and 80% of males with Becker's muscular dystrophy
- Nerve biopsy (rarely).
- Tensilon test.

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CK

- Serum CK measurement and EMG, which are very useful diagnostic tools in neuromuscular disorders
- Those are not particularly helpful for diagnosing congenital myopathy, because CK levels are usually normal or mildly elevated, while EMG can either be normal or not.
- CK assay are helpful in diagnosing congenital muscular dystrophies, metabolic myopathies, and some forms of the congenital myopathies.
- If serum CK is considerably increased up to 5-10 times compared to reference value, the clinician may suspect the diagnosis of DMD and Becker muscular dystrophy (BMD) spectrum as well as limb girdle muscular dystrophy and congenital muscular dystrophy, which needs further evaluation.
- The CK and iso-enzyme levels may be increased 10-fold for up to 1 week following normal vaginal delivery (presumably due to muscle trauma).
- The CK maybe even higher in the context of acidosis (e.g., severely asphyxiated newborns)
- However, serum CK can still be mildly elevated in neurogenic disorders as well.

J Genet Med 2018;15(2):55-63

Italian Journal of Pediatrics (2017) 43:10

Pediatr Neurosci. 2016 Jan-Mar; 11(1): 2–6.

EMG/NCV

- Electromyography (EMG) should not be performed in isolation.
- It does not allow for a definitive diagnosis as there are virtually no waveforms that are pathognomonic for specific disease entities.
- EMG is not advisable in case of suspected spinal muscular atrophy
- In the floppy child, EMG is helpful in deciding whether there is true weakness due to neuromuscular disease, or merely hypotonicity from causes in other systems or other parts of the nervous system.
- EMG is also useful to confirm a clinical suspicion of myotonia in the older child.
- NCV are useful in the investigation of hereditary motor sensory neuropathies and distinguishing axonal from demyelinating disorders.
- In myopathies, EMG shows low amplitude, polyphasic and short duration potentials, and in neurogenic disorders, NCS shows fibrillation potentials, positive sharp waves, fasciculation potentials and signs of reinnervation
- In myotonic disorders, EMG shows characteristic features of waxing and wane myotonic discharges with particular sound.

J Genet Med 2018;15(2):55-63

Italian Journal of Pediatrics (2016) 42:7

Residência Pediátrica 2018;8(supl 1):39-43

MUSCLE BIOPSY

- The role of muscle biopsy in the diagnostic workup of floppy infants is controversial.
- Muscle sampling is invasive, and often, results are not specific.
- Muscle biopsy remains the investigation of choice in an infant with a suspected congenital structural myopathy, as none of the clinical features are truly pathognomonic
- Muscle histology of SMA in the very first months of life of can be confusing;
- The most common histopathological diagnosis in the whole cohort was that of metabolic pathology and in particular a mitochondrial defect.
- If the clinician suspects a certain diagnosis with easier and less invasive genetic testing, muscle biopsy may not be necessary, such as in DMD, SMA, and FSHD.
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Front. Neurol. 2021; 12:735488.

J Genet Med 2018;15(2):55-63

Residência Pediátrica 2018;8(supl 1):39-43

MUSCLE BIOPSY AND PATHOLOGIC STUDIES

- By immunohistochemistry methods, one can assess absence, reduction or accumulation of certain proteins by labeling antibodies to specific proteins, for example absence of laminin α2 suggests underlying merosin-deficient congenital muscular dystrophy
- Fiber size and shape, fiber type pattern, position of nuclei in muscle cell, degeneration, regeneration, fibrosis and fatty change,, structural change, vacuole, enzyme deficiency, glycogen or lipid accumulation
- With electron microscopy, detailed examination of ultrastructure and organelle of the muscle fiber and identification vacuoles, rods, abnormal mitochondria or tubular aggregates
- These information can give clues to reach the diagnosis, yet not enough to confirm genetic change,
- As genetic and pathology overlap and heterogeneity in these disorders, again, necessitating further process of genetic mutation testing by panel.

J Genet Med 2018;15(2):55-63

MUSCLE AND BRAIN IMAGING: ULTRASOUND AND MRI

- Recently, muscle imaging including ultrasound and MRI is more widely used to differentiate different forms of congenital myopathy by evaluating selective muscle involvement pattern.
- Ultrasound has the advantage of easy utility in clinics not requiring sedation.
- MRI of the muscles not only shows extent of fatty changes within the muscle compartment but also shows specific patterns of involvement in the muscle groups, like in BMD and RYR1-related myopathy.
- The imaging studies are also used to choose appropriate muscle to proceed with biopsy.

• J Genet Med 2018;15(2):55-63

BRAIN MRI

- Brain MRI scan also shows significant pattern in some of the neuromuscular conditions in children.
- For example, merosin deficient congenital muscular dystrophy shows significant white matter signal changes, and in Fukuyama type of congenital muscular dystrophy and muscle-eye-brain disease, brain MRI shows occipital pachygyria.
- In Walker-Warburg syndrome, brain MRI shows severe lissencephaly.
- In mitochondrial disorders, unilateral or bilateral signal change in basal ganglia is quite significant in Leigh disease, and in mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes syndrome, acute focal lesions which occur in relation to stroke-like episodes, but occur outside the usual territories of vascular infarction are common

• J Genet Med 2018;15(2):55-63

NEW ERA OF MOLECULAR GENETIC TESTING

- There has been a huge improvement in the technique of molecular genetic diagnosis in this field for the past 15 years
- Techniques including multiplex ligation-dependent probe amplification (MLPA) and Sanger sequencing for specific genes are available.
- In disease groups like SMA and DMD with notable clinical presentation and history, MLPA method to detect exon deletion or duplication is the first-tier test.
- If MLPA is negative in DMD, then Sanger sequencing of the dystrophin gene will be the second-tier test, and for other disease groups with particularly well-defined clinical phenotype, Sanger sequencing is the cost-effective less time-consuming way to detect small sequence variation with higher diagnostic yield
- In other disorders there are advanced targeted gene panels, targeted next generation sequencing (NGS) or whole exome sequencing (WES) methods

• J Genet Med 2018;15(2):55-63

UTILITY OF METABOLIC SCREENING IN HYPOTNIA

- The central nervous system causes accounting for 60-80% of cases.
- Among central causes, chromosomal abnormalities and hypoxic ischemic encephalopathy (HIE) represent the most frequent etiologies, accounting for approximately 30% and 20% of neonatal hypotonia cases, respectively.
- Inborn errors of metabolism (IEM) comprise a rare subset of the conditions associated with hypotonia and/or global developmental delay (GDD).
- Studies have shown that biochemical testing for IEMs yields a diagnosis in a minority of patients (3—6%).
- In most case series have been shown that IEMs be considered only in cases of hypotonia and multi organ involvement.
- Despite these largely negative data, metabolic screening remains a recommended first-line test.

Annals of Clinical and Translational Neurology 2020; 7(7): 1132–1140

UTILITY OF METABOLIC SCREENING IN HYPOTNIA

- Screening metabolic laboratory tests typically include:
- plasma amino acids, urine organic acids, acylcarnitine profile, ammonium, Lactate and pyruvate
- It may extend to urine oligosaccharides, urine mucopolysaccharides, VLCFA, and studies of protein glycosylation,
- The Canadian Pediatrics Society position statement recommends a subset of metabolic screening laboratories as first-line investigations alongside chromosomal microarray, fragile X and brain MRI.
- Conversely, the American Academy of Pediatrics recommends against global screening, and rather recommends use of these investigations when there is clinical suspicion for an IEM.
- Despite this, it is still standard practice in US academic institutions to include metabolic tests when evaluating infants with hypotonia or GDD.

Annals of Clinical and Translational Neurology 2020; 7(7): 1132–1140

METABOLIC MYOPATHIES

- Metabolic myopathies (MMs) are a heterogeneous group of metabolic disorders characterized by defects of enzymatic pathways involved in myocyte metabolism
- MMs can affect the skeletal muscle exclusively, or the muscle plus other organs or tissues (metabolic myopathy plus (MM+), collateral myopathy).
- The limb muscles are predominantly affected in MM, but facial, extraocular, axial, and respiratory muscles may be additionally involved
- MMs manifest clinically as episodic conditions or as a permanent
- Episodic MMs may manifest during an episode with exercise intolerance, muscle cramps, myalgias, rhabdomyolysis, or myoglobinuria. Between the episodes, patients do not complain about muscle symptoms and the clinical neurologic exam is normal
- Permanent MMs manifest as muscle weakness, muscle wasting, exercise intolerance, easy fatigability, myalgias, sore muscles, muscle cramps, or permanent tiredness.

Life **2020**, 10, 43; 1-18

METABOLIC MYOPATHIES

- The most frequently disturbed metabolic pathways in muscle cells leading to MM are mitochondrial pathways, such as the respiratory chain (oxidative phosphorylation), or beta-oxidation, followed by cytoplasmic pathways, including glycolysis (Krebs cycle), glycogen synthesis, or lysosomal pathways, such as glycogen degradation (e.g., Pompe disease) and fat metabolism
- Classically, four categories of MMs are differentiated:
- I- MMs due to impaired carbohydrate metabolism
- II-MMs due to impaired lipid metabolism
- III- MMs due to impaired energy metabolism
- IV- MMs due to other impaired pathways
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Life **2020**, 10, 43; 1-18

METABOLIC MYOPATHIES

- When the episodes are triggered by short, intensive strain such as weight-lifting, sprinting or a “home run”, the underlying defect is most likely attributable to impaired glycogen metabolism
- When the episode is triggered by endurance exercise, such as hiking, biking, football, or even fasting, the underlying defect is most likely attributable to a fatty acid oxidation disorder (FAOD)
- Mitochondrial disorders (MIDs) frequently manifest as permanent MMs with exercise intolerance disproportionate with weakness, easy fatigability, myalgias and muscle cramps.

Life **2020**, 10, 43; 1-18

I-MM DUE TO IMPAIRED CARBOHYDRATE METABOLISM

- MMs due to impaired carbohydrate metabolism are subdivided into MMs with glycogen storage (muscle glycogen storage diseases (GSDs, glycogenoses) with or without the additional deposition of polyglucosan (glycogenoses)), and into MMs without glycogen storage (aglycogenoses),
- Sixteen different types of GSD are currently delineated, of which 11 manifest as MM or MM+
- The most common MM due to impaired glycogen metabolism is McArdle's disease.
- The only GSD that is treatable is Pompe disease (PD).
- The forearm ischemic exercise test relies on the determination of lactate and ammonia under ischemic conditions.
- Absence of an increase of serum lactate after resolution of ischemia is indicative of a GSD.
- In McArdle's disease, CK is permanently elevated, but it is only transiently elevated in phosphofructo-kinase deficiency

Life **2020**, 10, 43; 1-18

I-GSDS ASSOCIATED WITH MYOPATHY

Gene	Pathway	MM	MM+
GYS2	GSD 0	Yes	Yes (cardiomyopathy)
GAA	GSD II	Yes	Yes (cardiomyopathy, polyneuropathy)
AGL	GSD III	No	Yes (hepatopathy, cardiomyopathy, seizures, retardation)
GBE1	GSD IV	No	Yes (cardiomyopathy, hepatopathy)
PYGM	GSD V	No	Yes (retinopathy)
PFK	GSD VII	No	Yes (floppy infant, hemolysis)
PGAM2	GSD X	No	No
ALDOA	GSD XII	No	Yes (anemia, hyperkalemia)
ENO-3	GSD XIII	Yes	No
PGM1	GSD XIV	No	Yes (hypoglycaemia, hepatopathy)
GYG1	GSD XV (PGBM-2)	Yes	Yes (cardiomyopathy)
RBCK1	PGBM-1	Yes	Yes (cardiomyopathy, infections)

Life **2020**, 10, 43; 1-18

II-MMS DUE TO IMPAIRED LIPID METABOLISM

- MMs due to impaired lipid metabolism are a group of recessively inherited disorders due to either the defective import of long-chain fatty acids (LCFAs) into mitochondria (e.g., carnitine cycle disorder) or due to defective mitochondrial beta-oxidation (FAODs).
- Disorders of lipid metabolism may go along with lipid storage in muscle cells (lipid storage diseases/myopathies (LSMs)) or without intracellular lipid storage
- Clinically, lipid storage diseases are characterized by slowly progressive, fixed muscle weakness.
- Weakness can be seen in SLC22A5, ETFDH, CPT-II, primary carnitine deficiency (PCD), multi-acyl-CoA dehydrogenase deficiency (MADD), and neutral lipid storage disease with myopathy (NLSD-M)

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II-MMS DUE TO IMPAIRED LIPID METABOLISM

Gene	Location	Pathway	MM	MM+
SLC22A5	PCD	FA import	Yes	Yes (cardiomyopathy)
ETFDH	MADD	FAOD	Yes	Yes (skin disease, hepatopathy, hypoglycemia)
PNPLA2	NLSD-M	ATGL ↓	No	Yes (cardiomyopathy)
CPT2	CPT-II	FA import	Yes	Yes (encephalopathy)
HADHB	MTPD	Beta-oxidation	No	Yes (cardiomyopathy, neuropathy)
ACADVL	VLCADD	Beta-oxidation	No	Yes (cardiomyopathy, retardation, hepatopathy)
ECHS1	FAOD	Beta-oxidation	No	Yes (seizures, dystonia, developmental delay)

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III-MYOPATHY IN MITOCHONDRIAL DISORDERS (MIDS)

- The most well-known mitochondrial metabolic pathways involve the respiratory chain, but impairment of a number of other pathways may also go along with MM.
- Including MELAS, MERRF, KSS, Leigh syndrome, NARP, and chronic progressive external ophthalmoplegia (CPEO).
- Pediatric MIDs are more frequently due to mutations in nDNA located genes and adult-onset MIDs more frequently associated with mtDNA mutations
- However, a number of MIDs manifesting with isolated MM, particularly at onset of the disease,
- A cardinal feature of mitochondrial myopathy is easy fatigability, which is usually disproportional to the degree of muscle weakness.
- Frequently, MM in MIDs does not begin with weakness and wasting but with non-specific symptoms, such as myalgia, sore muscles, fatigue, muscle cramps, carpopedal spams, or exercise intolerance

Life **2020**, 10, 43; 1-18

MYOPATHY IN MITOCHONDRIAL DISORDERS (MIDS)

- The diagnosis of MIDs is based on clinical presentation, resting serum lactate and pyruvate, the lactate stress test, needle electromyography (EMG), muscle MRI, magnetic resonance (MR)-spectroscopy, muscle biopsy (including histological, immuno-histological, ultrastructural, biochemical, and polarographic investigations), and a genetic work-up.
- Normal muscle biopsy findings do not exclude the presence of a mitochondrial disorder (MID).
- Many patients complain about spontaneous muscle aching and sore muscles without previous muscle exercise.
- Fixed muscle weakness may first occur in the extraocular eye muscles or the lid elevators, leading to ptosis and external ophthalmo-paresis, but all other muscle groups may also be subsequently involved.
- Myopathy without involvement of the extraocular muscles may additionally occur
- Apart from limb muscles, axial and respiratory muscles may also be subsequently involved.
- Some patients may present with rhabdomyolysis

Life **2020**, 10, 43; 1-18

III-MYOPATHY IN MITOCHONDRIAL DISORDERS (MIDS)

Gene	Location	Pathway	MM	MM+
tRNA(Leu)	mtDNA	RC	No	Yes
tRNA(Lys)	mtDNA	RC	No	Yes
mtDNAΔ	mtDNA	RC	No	Yes
MPV17	nDNA	mtDNA depletion	No	Yes (hepatopathy, encephalopathy)
NDUFB8	nDNA	complex-I ↓	No	Yes (parkinsonism)
SLC25A1	nDNA	complex-V ↓	No	Yes (cognitive impairment)
HSPB8	nDNA	autophagy	No	Yes (neuropathy)
MRM2	nDNA	mt rRNA	No	Yes (MELAS-like)

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IV-OTHER MMS

- I) Lysosomal Storage Disease (LSD): include Pompe disease and Danon disease
- The lysosome-associated membrane protein-2 (LAMP2) encodes for a lysosome-associated membrane glycoprotein.
- LAMP2 is required for the maturation of autophagosomes by fusion with lysosomes. Thus, LAMP2 deficiency leads to failure and disturbance of macroautophagy .
- Mutations in LAMP2 manifest phenotypically with the characteristic triad of fixed, progressive, proximal myopathy, cardiomyopathy, and intellectual disability with onset in adolescence
- Myopathy in Danon disease may show a fluctuating course and may be easily misdiagnosed until a muscle biopsy shows typical vacuolar myopathy
- Cardiomyopathy in LAMP2 carriers may be associated with conduction defects, such as Wolf–Parkinson–White syndrome, which may be complicated by cardiac arrest secondarily leading to ischemic stroke
- Though Danon disease is an X-linked disorder, female carriers of the disease may be also affected, particularly in the heart . Rarely, Danon disease manifests without myopathy or mental impairment but exclusively with cardiomyopathy

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TAKE HOME MESSAGE

- The first step is to determine the area condition, either brain, spinal or motor unit.
- To definite diagnosis, neuroimaging, karyotype, and molecular testing should be used first line, whereas specific metabolic testing, nerve conduction study/Electromyography and muscle biopsy should be reserved as second line testing modalities
- Although metabolic disorders are well recognised as the cause for central hypotonia, because of the rarity of the conditions, the diagnostic yield is low unless is associated with GDD or multi organ involvement.
- With the advent of Next Generation Sequencing (NGS) testing has markedly improved over the last decade and this has had a unique impact on the evaluation of hypotonic infants.


THANK
YOU