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NpJSC Astana Medical University

Altynshash Jaxybayeva

THE COLLECTION OF NEUROMUSCULAR CASES: EDUCATIONAL AND PRACTICAL SYSTEM APPROACH

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J 11

REVIEWERS:
1**. I. Nishino** - Director of the Department of Neuromuscular Research, National Institute of Neurology and Psychiatry, Tokyo, Japan, Professor, Ph.D.
2. **D.N. Ayaganov** - Head of the Department of Neurology, West Kazakhstan Medical University, Aktobe, Ph.D.
3. **K.B.Manekenova** - Head of the Department of Pathological Anatomy, Medical University Astana, Professor, Ph.D.
4. **L.S.Kolyayeva** - Senior lecturer of the Department of Philological Disciplines, Master of Pedagogical Sciences

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The model of the assessment of clinical cases (collection of educational cases) presented in this book. This collection of cases is showing the complex approach to analysis of the information which could allow to make a precise diagnosis and choose appropriate line for management of rare neuromuscular diseases. This complex approach is demonstrating a way for avoiding diagnostic mistakes and misleading in treatment tactic**.** The author believes that it could guide medical professionals in everyday practice and health care managers in organization of the care for patients with rare pathologies.

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CONTENTS

LIST of ABBREVIATIONS

ALK - alkalkine phosphate stain - familial ALS (fALS)- familial amyotrophic lateral sclerosis
ATP- adenosine triphosphate
CBM - cytoplasmic body myopathy
CK- creatine phosphokinase
CM – congenital myopathy
CMT - Charcot–Marie–Tooth
CP -cerebral palsy
CPEO - Chronic progressive external ophthalmoplegia
CT- computed tomography
DMAT - Distal myopathy with anterior tibial onset
DMD/BMD - Dushenne muscular dystrophy/ Becker muscular dystrophy
DTRs - deep tendon reflexes
ECG - electrocardiography
EDMD – Emery Dreifuss myodystrophy
EMG - elecromyography
H&E – hemotoxiline and eosin stain
HIBM - hereditary inclusion body myopathy
HMERF - Hereditary myopathy with early respiratory failure
HMSN - Hereditary motor and sensory neuropathies
IBM - Inclusion body myositis
IIM - Idiopathic Inflammatory Myositis
IMNM - immune-mediated necrotizing myopathy.
IU/L - international units per liter
IVIG – intravenous immunoglobulin
MELAS - Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
MERRF - Mitochondrial Encephalopathy with Ragged Red Fibers
mGT – gomori trichrome stain
MRI – magnetic resonance imaging
NCNP - National Center of Neurology and Psychiatry
nEMG – electromyography
NMD – neuromuscular diseases
RRF- raged red fibers
RYR1- ryodine 1 receptor
SDH (succinate dehydrogenase) staining
SMA - Spinal muscular atrophy
TTN- titine
VC – velocity conduction

Preface and Acknowledgements

The collection of educational cases on some neuromuscular diseases were a result of my three months stay at the National Center of Neurology and Psychiatry (NCNP) which located in the suburb of Tokyo. These three months stay was supported by the research grant from Matsumae Foundation and devoted to the implementation of the project aimed to the investigation of the way on establishment of centralized diagnostic system of muscle diseases in Kazakhstan.

NCNP was established in 1986, as one of the six national centers in Japan. This center is the world unique center and called "The only Flower in the World". The basic concept of this center is that the hospital and research institutes work together to conduct research and development aimed at overcoming mental, neurological, muscle diseases, and developmental disorders, and provide advanced pioneering medical care based on the research results and disseminate high quality care throughout the whole country and other Asian regions.

NCNP functions as a nationwide referral center for muscle disease and approximately 80% of muscle biopsy samples are sent there for diagnostic purpose from all over Japan. For diagnosis, NCNP conducts a full battery of histochemical and immunohistochemical stains for virtually all cases to provide pathological diagnosis, in addition to genetic analysis using next-generation sequencing technology. For rare disorders like muscle disease, this type of centralized diagnosis system is the most efficient, as evidenced by the fact that most developed countries have such centers. Furthermore, the NCNP Hospital follows the largest number of neuromuscular patients in Japan. The department of Neuromuscular Research which is part of NCNP definitely is a right and best place to learn about organization of neuromuscular service.

The best way to share an experience and knowledge is a demonstration of existed practice. The systematical approach of complex assessment of the neuromuscular cases which is developed in NCNP became a basis for the writing this collection of cases in order to show the example of them and attempt to analyze a good research and clinical practice. I do hope that this practical collection of cases may become a guide to the establishment of neuromuscular research and good clinical practice in Kazakhstan and also play a valuable and educational role for the medical specialists.

The data of clinical material including biopsy illustrations has come from the National Center of Neurology and Psychiatry. I am grateful to the Director of the Department of Neuromuscular Research prof. Ichizo Nishino, research fellow/scientists Yushihiko Saito, Yukako Nishimori, Nobuyuki

Eura, Hayato Une, Wakako Yoshioko and other colleagues for providing me all necessary information. I am particularly appreciating secretary staff of the Department of Neuromuscular Research for the facilitation of my work. Also, I am appreciating clinical colleagues Dr. Yuko Shimizu-Motohashi, Dr. Madoka Mori and Dr. Hirofumi Komaki who is the General Director of Translational Medical Center, and Director of Muscular Disease Center, who shares their knowledge and demonstrating me a practical clinical approach. I would like to express my deep respect to the Honorary Member of the Department of Neuromuscular Research Prof. Ikuya Nonaka, who is a prominent pediatric neurologist and one of the founders of neuromuscular research in the world who began development of this systemically approaches.

All of them allow me to learn not only basic approaches to muscle pathology but also the way of systematic assessment of neuromuscular diseases.

Introduction:

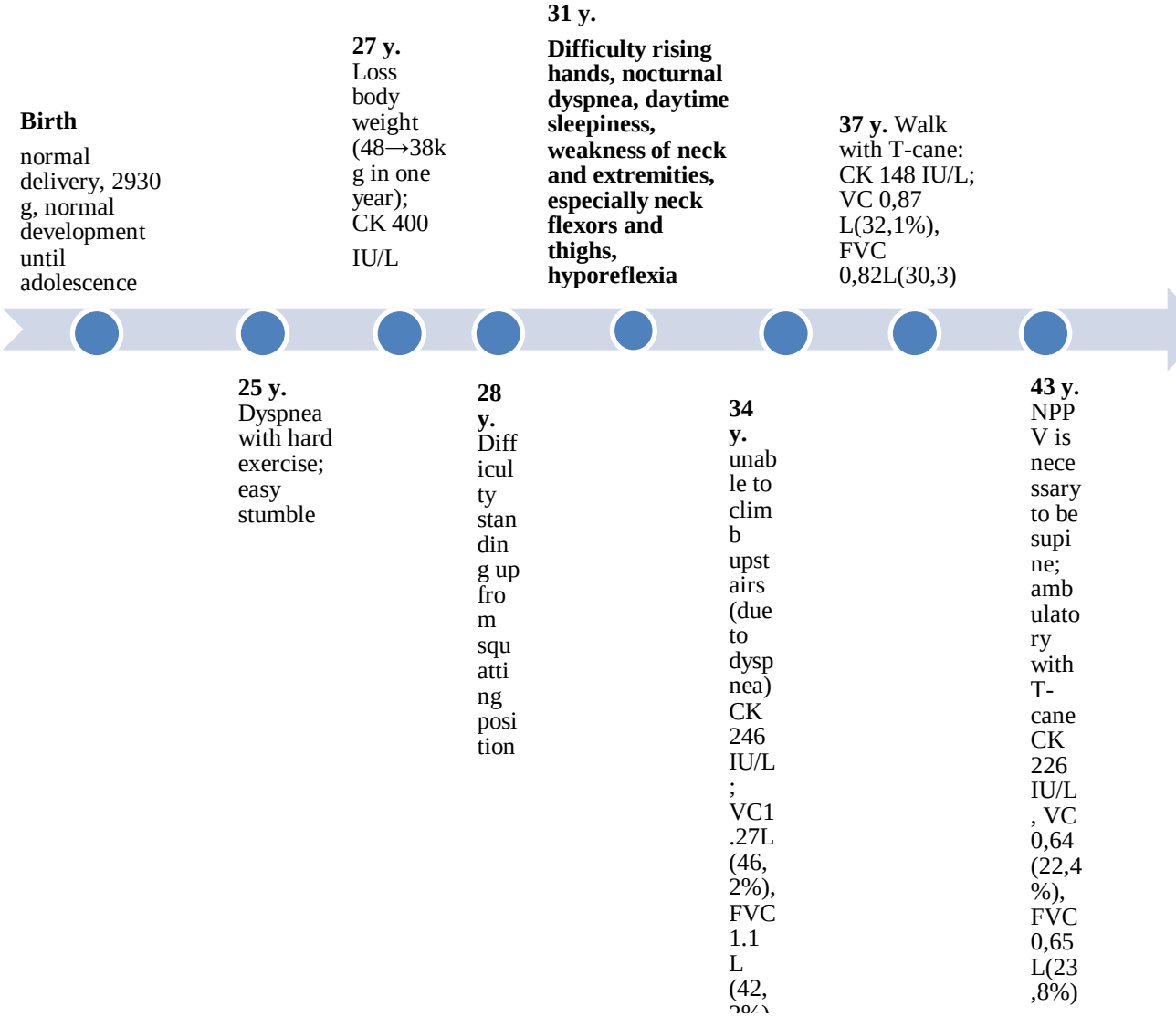
Muscle disease is a group of rare but heterogeneous disorders. The onset of the diseases ranges widely from birth to elderly. Many of these diseases are life threatening and progressive. This is a very much specialized field for which specific knowledge and experiences are necessary. In reality, however, many medical professionals are not familiar with neuromuscular conditions, naturally leading to wrong diagnoses and inappropriate managements. In Kazakhstan, it is a burning issue now due to an increasing number of patients with muscle diseases although the alertness at doctors is virtually lacking regarding this rare condition. Many of these patients have wrong diagnosis like cerebral palsy and have been treated more aggressively than needed. In Kazakhstan, international guidelines for diagnostic and treatment approaches to Duchene muscle dystrophy and spinal muscular atrophy were just recently accepted, and we started to give patients more or less proper care including hormones, respiratory and nutritional support. Nevertheless, other types of muscle diseases are still underdiagnosed or even undiagnosed due to lack of knowledge and absence of system for neuromuscular service in Kazakhstan. Proper diagnostic and management for such kind of rare diseases are mostly dependent on the growth of scientific knowledge and the development of new therapies. Importantly, the status of some of those diseases are now moved from the untreatable to treatable side. Needless to say, it is very important to establish a system for muscle diseases in order to provide proper health care to patients through scientifically-proven approaches, such as imaging, immunohistochemistry, and molecular studies.

Therefore, the model of NCNP should be one of the best models for Kazakhstan to establish a similar nationwide neuromuscular center within the country. The model of the assessment of clinical cases (collection of educational cases) presented below. This collection of cases is showing the complex approach to analysis of the information which could allow to make a precise diagnosis and choose appropriate line for management of rare neuromuscular diseases. This complex approach is demonstrating a way for avoiding diagnostical mistakes and misleading in treatment tactic. The author believes that it could guide medical professionals in everyday practice and health care managers in organization of the care for patients with rare pathologies.

Case 1. Case of hereditary myopathy with early respiratory failure
Description of the case: 31 y, female
Chief complaints: dyspnea and weakness of limb and neck
Family history: No NMD, no consanguinity
Status presence: 150sm, 40 kg;
CK488 IU/L, aldolase 7,7 IU/L, lactate 13,7 mg/dL; pyruvate 0,91 mg/dL;
BGA(room air):pH 7,3; pCO2 79,9 mmHg, pO2 41,7 mmHg, HCO3 38,2, BE+11,6
VC 0,89L(31,8%), FVC 0,89L(31,8%)
nEMG: diffuse myogenic pattern
Muscle biopsy was provided
NPPV, oral steroids stated

The history of the illness

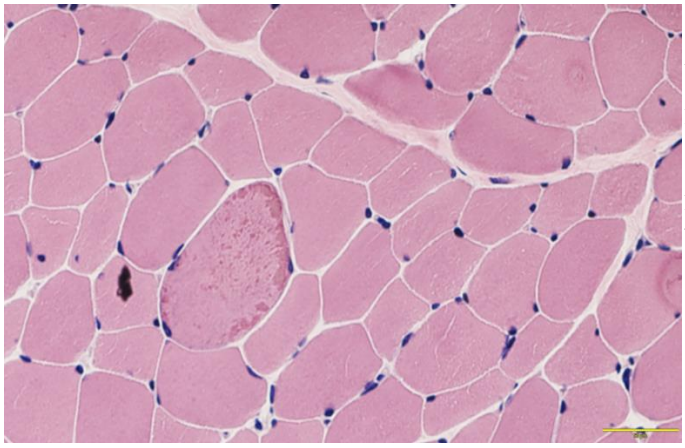
Scheme1.



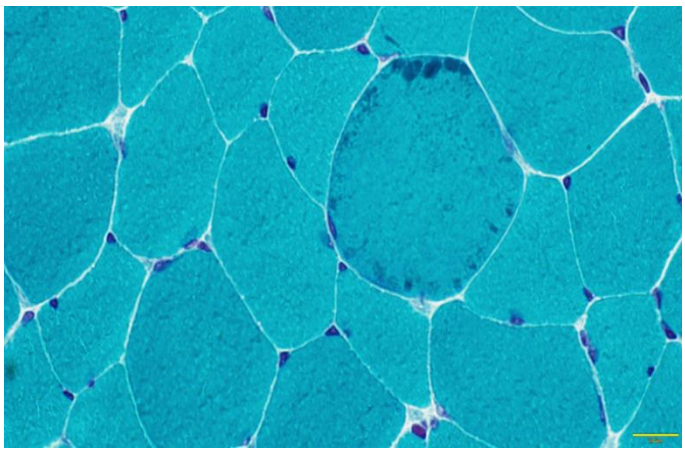
Key findings from the case description	Suspected disease
Dyspnea and muscle weakness from 25 years→31y→43 years (**gradually increased**) Loss body weight **Weakness of neck flexors and thighs** **Hyporeflexia** **CK slightly elevated** (max 488 IU/L) **Respiratory failure:** lactate elevated 13,7 mg/dL; BE +11,6; pH 7,3; pCO2 79,9 mmHg, pO2 41,7 mmHg, HCO3 38,2, VC 0,89L(31,8%)	Myopathy Myasthenia Mitochondrial disease

Table 1.

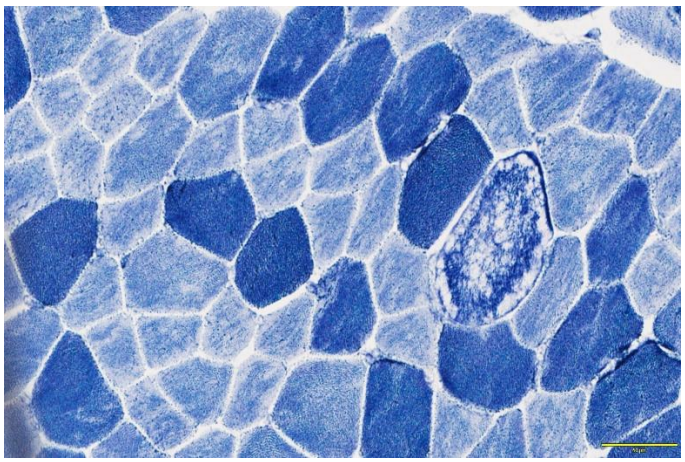
Muscle biopsy findings (Pic.1)



Pic.1.1. H&E: fiber type variation is mild to moderate. Endomysial fibrosis is not seen; no necrotic and scattered basophilic fibers are seen, one fiber with membrane inclusions



Pic.1.2. On mGT: cytoplasmic bodies in periphery of fiber are seen, RRFs is not seen



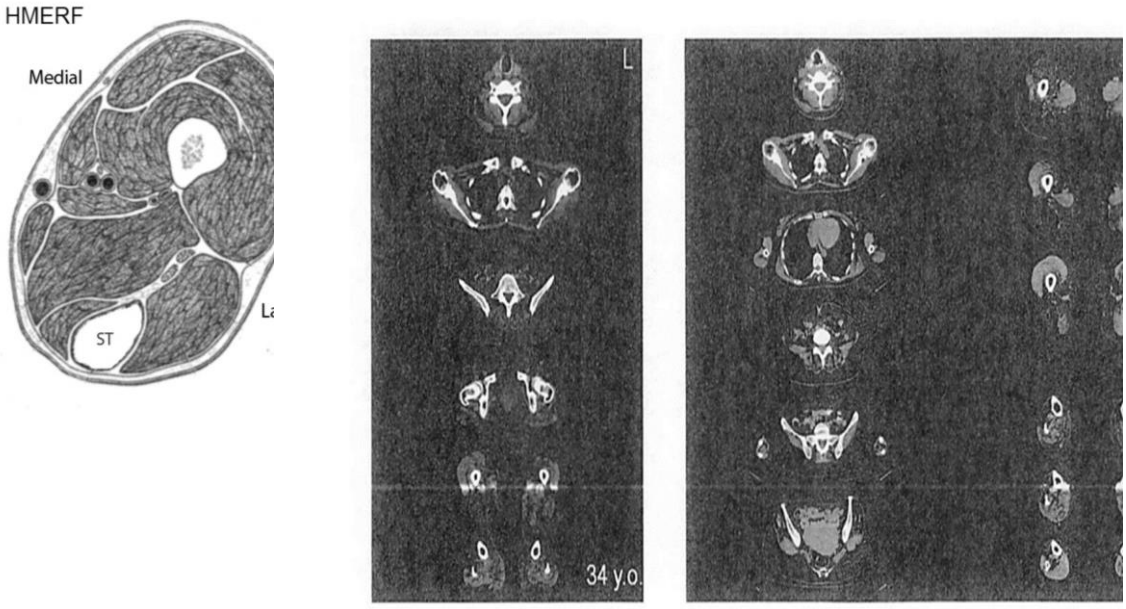
Pic.1.3. On NADH: the intermyofibrillar network is disorganized in some fibers

Pathological diagnosis

1. Myopathic changes with:
2. Variation in fibers size, mild to moderate
3. Regenerating fibers, a few
4. **Fiber with necklace cytoplasmic bodies**, one
5. Type 1 fiber predominance and type 2 C fibers, a few
6. Type 2 fiber atrophy, mild to moderate

The above findings reflect to myopathic process and one fiber with inclusions is seen.

Muscle imaging data of the patient in comparison with reference scheme.



Pic.1.4.

Summary of complex analysis of all findings:
Dyspnea and muscle weakness
from 25 years→31y→43 years (**gradually increased**)
Loss body weight
Weakness of neck flexors and thighs
Hyporeflexia
CK slightly elevated (max 488 IU/L)
Respiratory failure: lactate elevated 13,7 mg/dL; BE +11,6; pH 7,3; pCO2 79,9 mmHg, pO2 41,7 mmHg, HCO3 38,2, VC 0,89L(31,8%)
Cytoplasmic body inclusions (Fiber with necklace cytoplasmic bodies)
MRI: involvement of semitendinosus, sartorius and gracilis muscles
All above findings suggested to Hereditary myopathy with early respiratory failure (HMERF)

Literature review: Lars Edström and coworkers described HMERF in 1990.

The authors reported 16 patients from 7 Swedish families characterized by the following clinical and laboratory features:
1) respiratory failure, often developing sub acutely and frequently being the symptom at onset of the disease;
2) limb-girdle distribution of muscle weakness accompanied by foot extensor and neck flexor weakness;
3) myopathic findings on electromyography and normal or slightly elevated serum creatine kinase level;
4) absence of neuropathy and heart involvement;
5) autosomal dominant mode of inheritance of the disease, with onset between the second and the fifth decade.

On muscle biopsy, the hallmark of HMERF was the presence of circumscribed “plaques” which were eosinophilic on hematoxylin and eosin and stained red, purple or dark green on Gomori trichrome.

Some other reported patients were classified as cytoplasmic body myopathy (CBM) with respiratory failure but no genetic data have been published on these patients [1].

Muscle imaging findings

Early involvement: semitendinosus and obturator externus

Relative sparing: biceps femoris and semimembranosus.

The other most affected muscles: iliopsoas, gracilis, anterior leg muscles and, peculiarly, popliteus.

Notably, in this first study the authors already hypothesized the use of MRI for the discovery of new families or sporadic cases with HMERF and the testing

of oligosymptomatic individuals, with implications on respiratory follow-up [2,3].

Molecular genetical findings

1. Titin was considered a strong candidate for the disease, and one single change in titin, co -segregating with the disease.
2. Titin is actually the biggest protein in the human cells and in nature. TTN has 364 exons.
3. This makes it approximately 8 times bigger than DMD, the dystrophin gene.
4. Titin is a structural protein.

Summary:

1. The **presence of cytoplasmic bodies**, the **early respiratory involvement** and the **absence of cardiomyopathy** should suggest a diagnosis of **Hereditary myopathy with early respiratory failure.**
2. Cytoplasmic bodies is still the most useful pathological sign to address the genetic testing towards HMERF rather than other myofibrillar myopathies.
3. Clinicians should ruled out other possible clinical overlaps that could present with marked respiratory involvement in ambulant patients such as congenital myopathies like late-onset nemaline myopathy, acid maltase deficiency, inflammatory myopathies (anti Jo-1 myopathy), muscular dystrophies due to lamin A/C gene mutations, and to a lesser extent sarcoglycanopathies, LGMD2A and LGMD2I.
4. The advisable molecular diagnostic algorithm includes at least the sequencing of TTN exon 344 in suspect cases.

Case 2: Case of LMNA myopathy

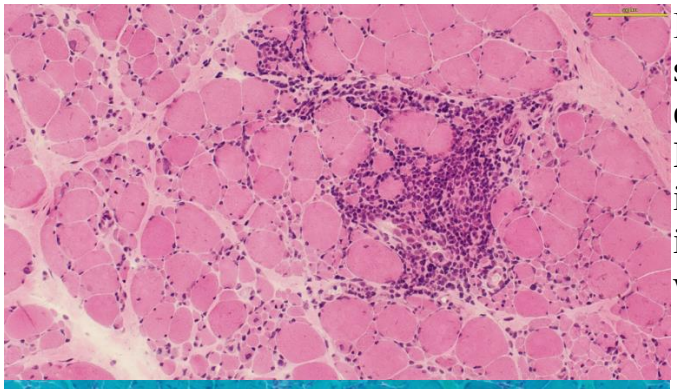
Description of the case : 1 y 6 m, boy
Chief complaint: no ambulance at 1 y 6 m
History of present illness: born at 38 weeks of gestation without any complication. BW was 2880 grams. At medical check-up at 1 y 6 m, he was pointed out to be still non-ambulant.
Past medical history: unremarkable
Family history: no neuromuscular disease, no consanguinity
Physical examination: no muscle weakness. Normal muscle tone.
Laboratory data: CK:1072IU/L (normal :51-197)
ECG: normal
Muscle immunohistochemistry: all normal including dystrophin, sarcoglicans, alpha-dystroglycan, laminin 2, caveoline-3, dysferlin, collagen VI, and emerin.

Key findings: developmental delay (non ambulant at 1y6m) and elevated CK 1072 IU/L (normal 51-197)

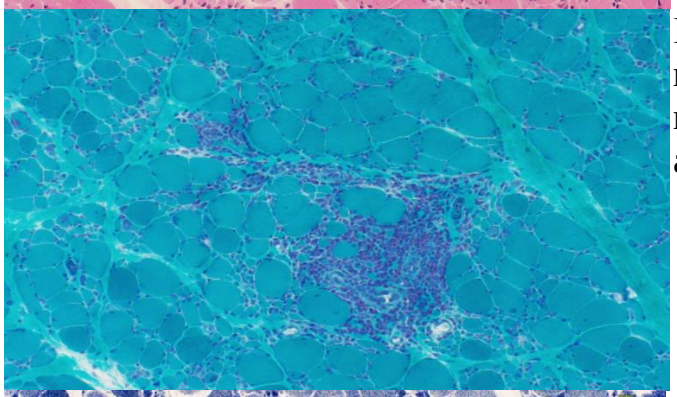
Creatine kinase level	
Normal or mild elevation (2-5x normal)	Congenital myopathies; lamin A/C EDMD, neurogenic disorders (SMA3), mitochondrial myopathies, inflammatory myopathies
Moderately elevated (5-10x normal)	Many myopathies and dystrophies, inflammatory myopathies
Very high (over 50x normal)	DMD/BMD, dysferlinopathy, calpainopathy, ANO5, sometimes in inflammatory myopathies

Table 2.1.

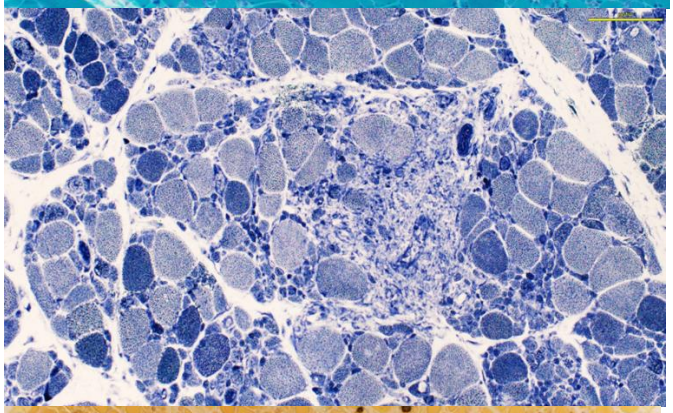
Muscle biopsy data (Pic.2)



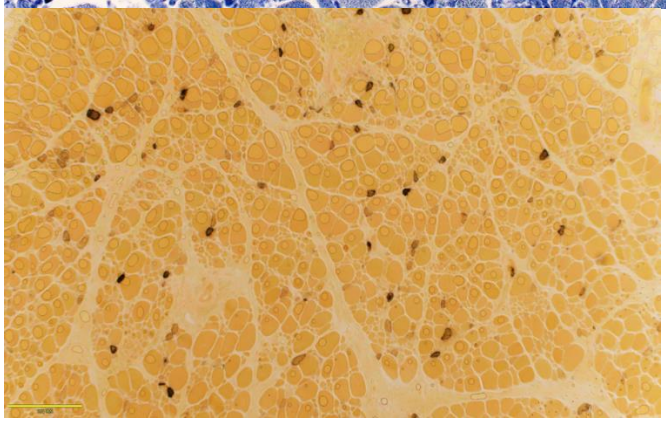
Pic.2.1. On H&E: marked size variation, mild endomysial fibrosis is seen. Mononuclear cell infiltration is seen in endomysium only in one fascicle. Some fibers with centralized nucleus.



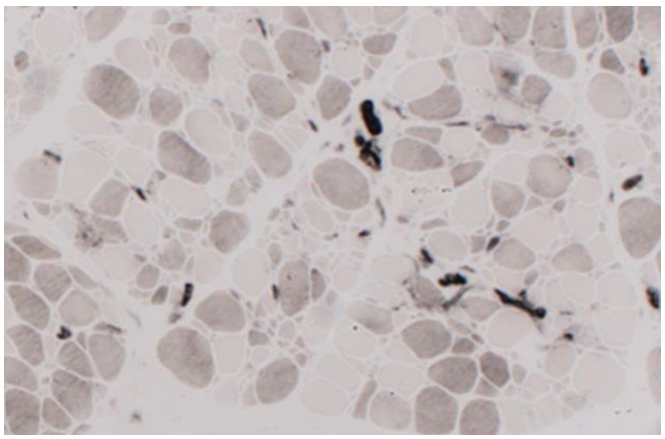
Pic.2.2. On mGT: ragged-red fibers(RRFs), nemaline rods and rimmed vacuoles are not seen



Pic.2.3. On NADH: intermyofibrillar networks are well organized except in atrophic fibers



Pic.2.4. On ALK: enzyme activity is increased mainly in regenerative fibers



Pic.2.5. On ATP: type 1 and 2 fibers with the same size

Pathological diagnosis:

Nonspecific change with:

1. Fiber size variation, marked
2. Mononuclear cells infiltration, seen
3. Endomysial fibrosis mild
4. Fibers with internal nuclei, some

The present biopsy reflects to chronic muscular pathology.

Possibility of inflammatory myopathy should be excluded [4].

Genetical analysis should be recommended **LMNA gene mutation founded.**

Literature review:

Laminopathies belong to rare inherited human diseases.

The most frequent are mutations in the LMNA gene, that encodes two proteins: lamin A and lamin C, which are responsible for the maintenance of nuclear shape, resistance for mechanical stress and cell cycle regulation through their interaction with chromatin and transcription factors.

Variants in the LMNA gene, encoding lamin A/C, are responsible for a growing number of diseases.

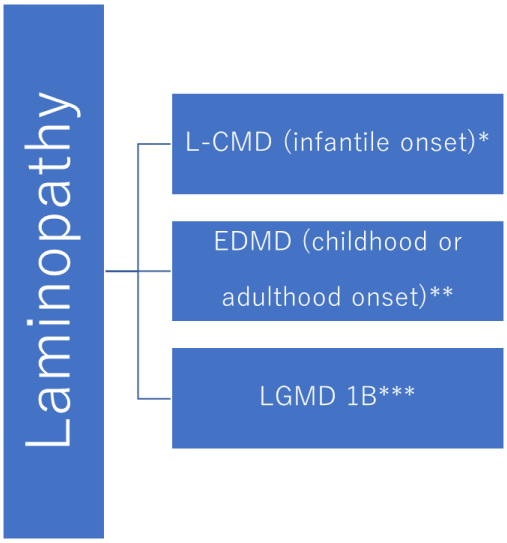
LMNA-related disorders have a varied phenotypic expression with more than 15 syndromes described, belonging to five phenotypic groups[5,6]:

- Muscular Dystrophies,
- Neuropathies,
- Cardiomyopathies,
- Lipodystrophies
- Progeroid Syndromes.

Overlapping phenotypes are also reported.

Laminopathies – muscular dystrophies［7,8,9］

Congenital muscular dystrophies associated with nuclear membrane proteins



Scheme 2.

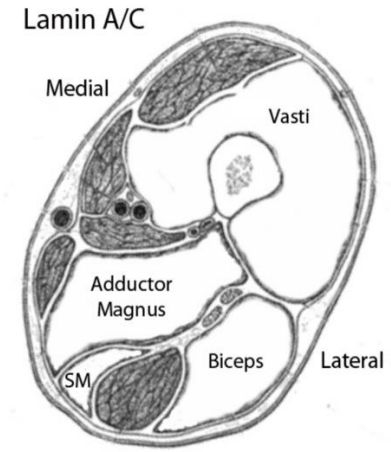
Presented at birth and classified as a congenital muscular dystrophy.

Respiratory insufficiency can be rapidly progressive, and spinal rigidity and scoliosis typically develop. Neck weakness resulting in a “dropped head” may also be a feature, although not specific for lamin A/C mutations.

Serum CK levels are mild to moderately elevated.

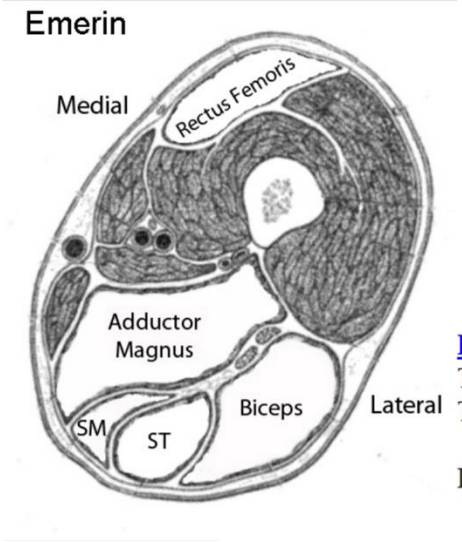
Muscle pathology is variable and may be mild. Features that may be present include variation in fiber size and increase in connective tissue, inflammation, necrosis, and regeneration. No immunohistochemical abnormalities on sarcolemmal proteins or nuclear proteins are seen. But HLA-ABC is positive which could be mimic with myositis (IMNM)[10].

Muscle MRI findings at EDMD［https://neuromuscular.wustl.edu］



LGMD 1B; EDMD2
Trunk
Common: Paraspinal (Multifidus & Longissimus)
Uncommon: Abdominal
Pelvis
Common: Gluteus minimus & medius
Uncommon: Psoas
Thigh
Common: Posterior; Adductor major
Uncommon: Sartorius; Gracillis
Hypertrophic: Rectus femoris
Leg Common & Early: Gastrocnemius, medial
Often: Gastrocnemius, lateral; Soleus
Uncommon: Anterolateral, less than EDMD1

Pic.2.6.



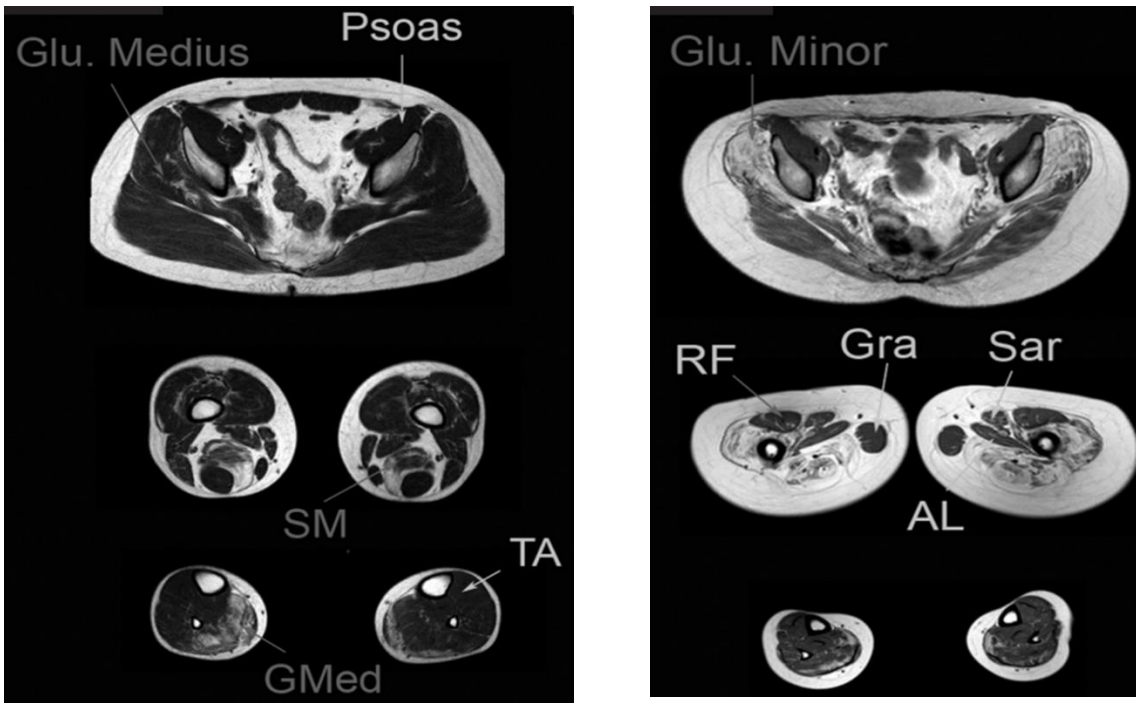
EDMD1
Trunk Paravertebral, Glutei
Thigh Quadriceps, Semitendinosus, Semimembranosus, Biceps femoris, Adductor magnus
Leg Soleus, Gastrocnemius, Peronei

Pic.2.7.

Muscle MRI of two patients with mutations in the LMNA gene[11]

Patient with mild weakness. In this patient we observed fatty infiltration in the gluteus medius, semimembranosus (SM) and gastrocnemius medialis (GMed) muscles

Patient with severe weakness: fatty infiltration was observed in gluteus minimus and medius. All the muscles of the thighs were involved, except rectus femoris (RF), adductor longus (AL), sartorius (Sar) and gracillis (Gra) that were not atrophic.



Pic.2.8.

Summary of complex assessment:

These LMNA-muscular dystrophies differ in the age at onset of the muscular symptoms, the degree of joint contractures, when present, and, the severity, progression rate and topology of muscle wasting and weakness.

But they all share a common feature, i.e. a life-threatening cardiac disease characterized by conduction and/or rhythm defects associated with dilated cardiomyopathy resulting in a high frequency of cardiac sudden death*.

LMNA mutation should be considered in myopathy patients with inflammatory changes during infancy, and that this may help avoid life-threatening events associated with laminopathy

There is scarce evidence that steroid therapy may bring some motor improvement.

A major LMNA-associated clinical problem is represented by the phenotypes that induce the risk of sudden cardiac death due to malignant arrhythmia

Cardiac transplantation extends survival. Early referral for heart transplant is therefore advised in laminopathies.

Atrial fibrillation and other atrial arrhythmias are common manifestations of laminopathies. They have been associated with high risk of stroke and other cardioembolic complications, therefore requiring the systematic use of curative anticoagulation, regardless to CHADS-VASC score [12,13,14].

Case 3. Case of proximal myopathy (congenital muscular dystrophy or inflammatory myopathy)

Description of the case: **16 y, female**

1. **Chief complaint:** Gait disturbance
2. **Past medical history: N**egative
3. **Family history: N**o neuromuscular disease
4. **Physical examination:** she had marked, predominantly proximal, muscle weakness and atrophy, sparing facial muscles. Distal muscle strength was reported to be normal. No calf hypertrophy or atrophy was seen. Gowers` sign was positive. She had waddling gait. DTRs were decreased. Dysphagia or dysarthria was not seen.
5. **Laboratory data:** CK 7930 IU/L (normal 45-163) **Autoantibodies:** Jo-1(-), ANA(-)
6. **EMG:** Early recruitment, fibrillation and positive sharp waves, low polyphasic units. CRD in some muscles.
7. **ECG:** normal

History of the illness

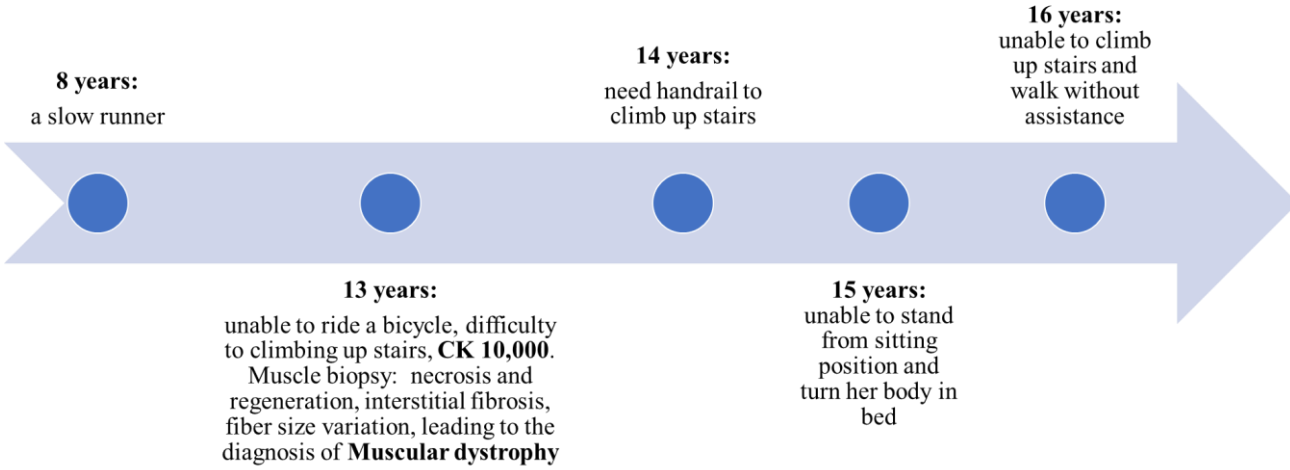
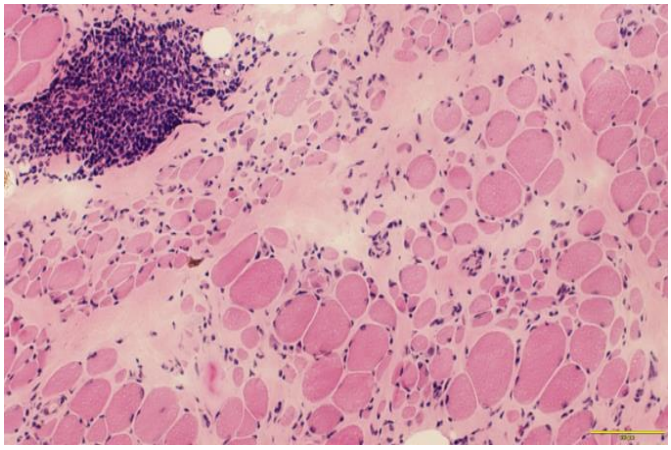
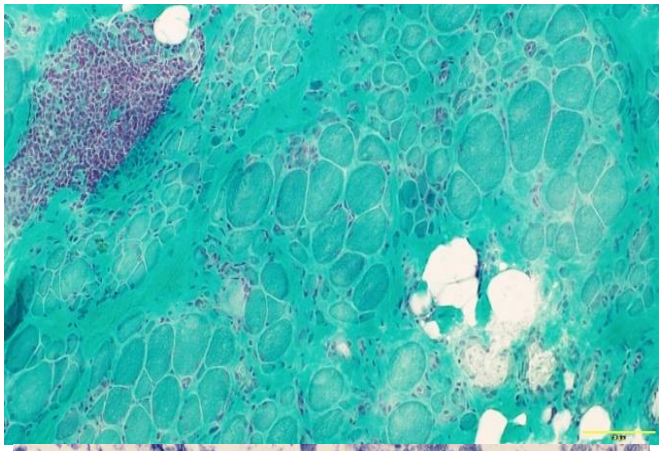


Table 3.1.

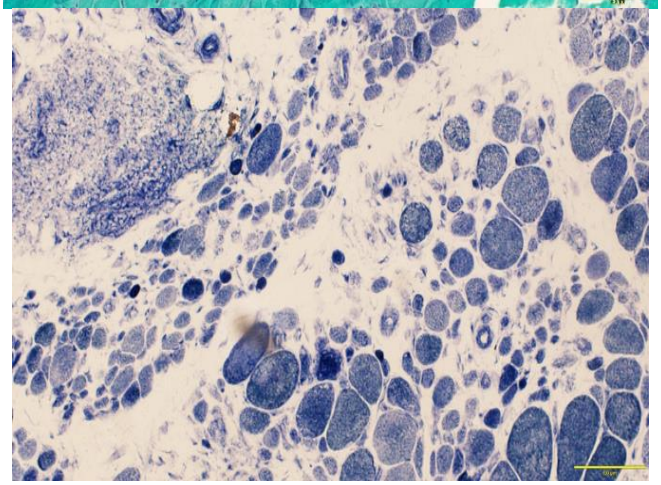
Muscle biopsy data (Pic.3)



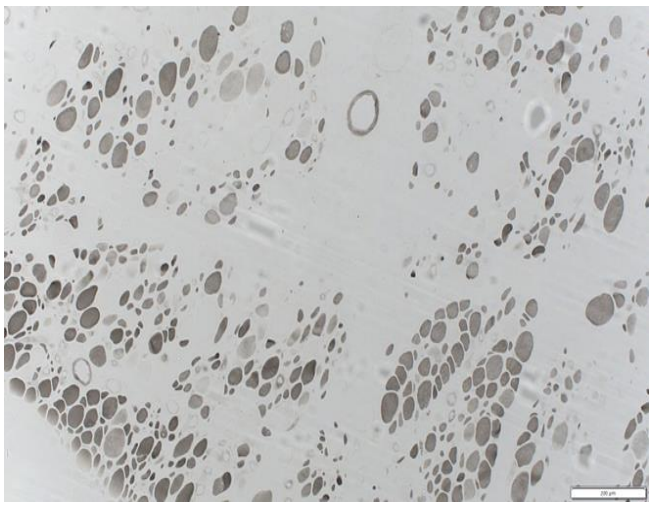
Pic.3.1. H&E: there is marked variation in fiber size measuring from 20 to 100 micron in diameter. A necrotic and regenerating fibers are scattered. Some fibers have internal nuclei. Moderate endomysial fibrosis is seen. Adipose tissue infiltration is seen



Pic.3.2. On mGT, ragged-red fibers(RRFs), nemaline rods and rimmed vacuoles are not seen. Peripheral nerve is well myelinated

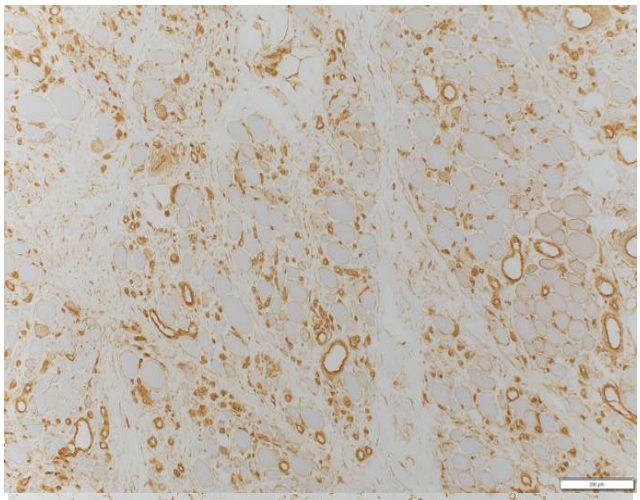


Pic.3.3. On NADH-TR, intermyofibrillar networks are mildly disorganized, showing moth-eaten appearance in type1 fibers.

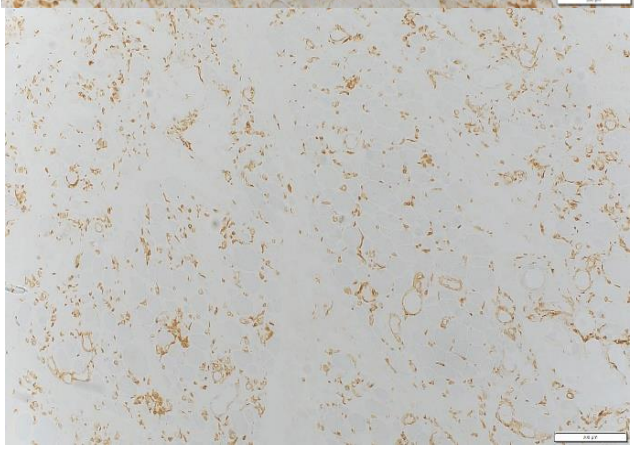


Pic.3.4. On ATPase, fiber type grouping is not seen. Type 2c fibers are scattered. Marked type 2 fibers atrophy is seen

Immunohistochemistry



Pic.3.5. HLA-ABC: positive



Pic.3.6. HLA-DR: negative

Pathological diagnosis:

Myopathic changes with:

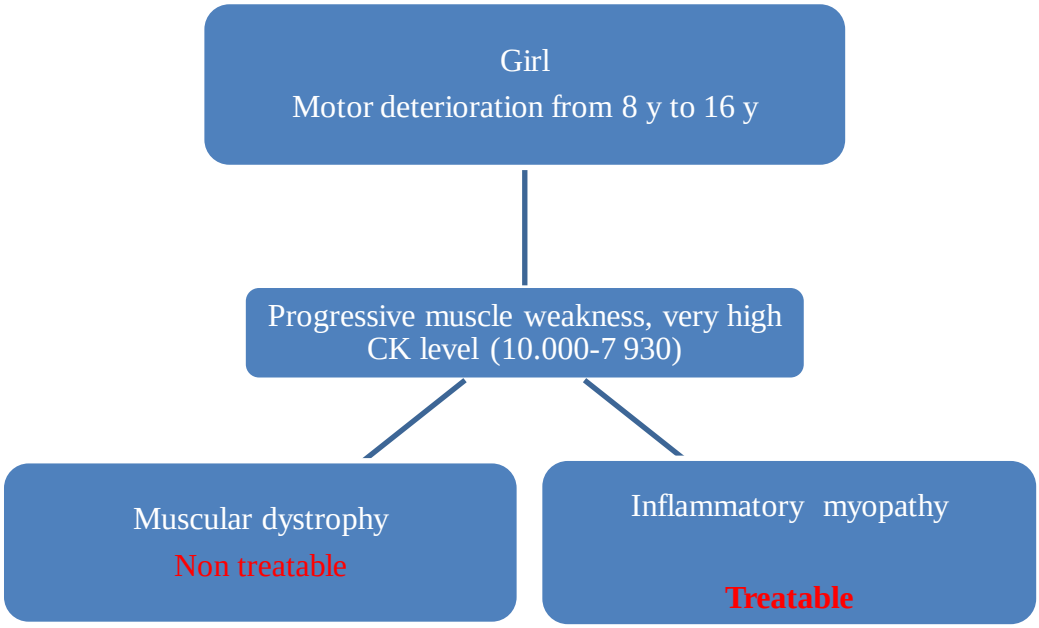
1. Variation in fiber size, marked
2. Necrotic and regenerating fibers, scattered
3. Fibers with internalized nuclei, some
4. Endomysial fibrosis, moderate
5. Type 2 c fibers, marked

The above findings are suggestive to chronic myopathic changes with necrotic and regenerating process.

HLA-ABC positive and HLA-DR negative on IHC.

And we have to check antibodies for myositis **HMGCR(+)** IMNM-immune-mediated necrotizing myopathy.

Why is important to know exact diagnosis in this particular case?



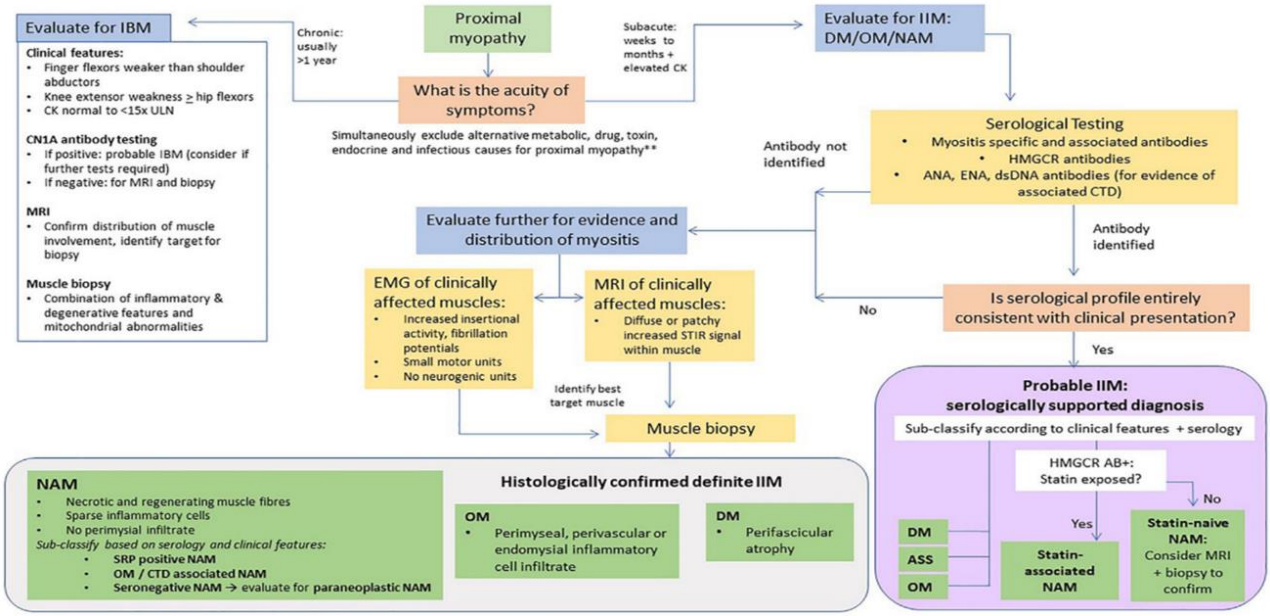
Scheme 3.1.

Differential diagnosis

	Prons	Cons
Muscular dystrophy	Gait disturbance, Muscle weakness, positive Gowers' sign. Waddling gait, decreased DTRs. CK 10,000-7,930 IU/L; Autoantibodies: Jo-1(-), ANA (-) Muscle biopsy: necrosis and regeneration, interstitial fibrosis, fiber size variation	Sparing facial muscles. No calf hypertrophy or atrophy was seen.
Inflammatory myopathy (myositis)	Gait disturbance, Marked, predominantly proximal, muscle weakness and atrophy, positive Gowers' sign, Waddling gait. Decreased DTRs. CK 10,000-7,930 UI/L; Muscle biopsy: necrosis and regeneration, interstitial fibrosis, fiber size variation, some fibers with internalized nuclei	No dysphagia or dysarthria. Autoantibodies: Jo-1(-), ANA(-)

Table 3.2.

Diagnostical Algorithm for proximal myopathies[15]



Scheme 3.2.

Clinicoseropathological characteristics in major subgroups of idiopathic inflammatory myopathies[16]

IIM subgroup	Associated antibody	Clinical features and associated HLA haplotye (s)	Pathological features: Histological features	Immunohistochemical features: HLA-ABC	HLA-DR	C5b-9	Note
DM	Anti-TIF1-γ	CAM (≥39 years of age) Severe skin erythema HLA-DQB1*02:01 (JDM) HLA-DQB1*02:02 (adult)	PFA, punched-out vacuoles mild lymphocytic infiltrate	+	−/+	Capillaries+++ Sarcolemma +	Typical skin lesion in DM: Gottron sign, Gottron papules, heliotrope rash PF-COX paleness can be present in all DM, less present in anti-MDA5 All DM show sarcoplasmic MxA positivity
	Anti-Mi-2	Prominent muscle involvement HLA-DRB1*07:01 HLA-DRB1*03:02	PFA, PFN, perimysial connective tissue, fragmentation, PF-ALP, B cells and B cell clusters can be present	+	−/+	Sarcolemma +++ capillaries +/−	
	Anti-NXP-2	JDM, DMSD, CAM, calcinosis, muscle ischemia, skin edema	Microinfarction	+	−/+	Capillaries ++ Sarcolemma +	
	Anti-MDA5	ADM, RP (fatal)-ILD in 1/3 of patients, mucocutaneous ulceration, palmar papules, nonscarring alopecia, panniculitis HLA-DRB1*01:01 HLA-DRB1*04:05 HLA-DRB1*12:02	Non-PFA	+	−/+	Capillaries + Sarcolemma+/−	
	Anti-SAE	ILD	PFA	+	−/+	Capillaries	
ASS	Anti-Jo-1	Myositis >ILD HLA-B*08:01 HLA-DRB1*03:01	Myofiber necrosis and regeneration, PFN, perimysial connective tissue, fragmentation, PF-ALP,	+	+ (PF)	Sarcolemma	ASS: Various combination of: myositis, ILD, Raynaud phenomenon mechanic's hands, joint involvement, fever
	Anti-PL-7	ILD >myositis		+	+ (PF)	Sarcolemma	
	Anti-PL1−2	ILD >myositis		+	+ (PF)	Sarcolemma	
	Anti-OJ	Severe muscle involvement in early stage		+	+ (PF)	Sarcolemma	
IMNM	Anti-SRP	Risk cardiac involvement HLA-DRB1*08:03	Myofiber necrosis and regeneration, sparse inflammation (macrophages > lymphocytes)	+	-	Sarcolemma	IMNM: p62 diffuse tiny dots
	Anti-HMGCR	CAM? HLA-DRB1*07:01 (juvenile) HLA-DRB1*11:01 (adult)		+	-	Sarcolemma	
	Seronegative IMNM	CAM		+	−/+	Sarcolemma	
IBM	AnticN1A?	Frequently asymmetrical weakness, knee extensors, finger flexors >45 years of age (younger in virus-associated IBM) HLA-DRB1*03:01 HLA*08:01	H&E: lymphocytic invasion in endomysium and nonnecrotic fibers mGT: rimmed vacuoles COX: COX-negative fibers Tubulofilaments in vacuoles and/or in nuclei	+	+	+/−	p62 discrete subsarcolemmal, perivacuolar area CD8 endomysial, nonnecrotic fibers invasion Highly differentiated T- cells

Table 3.3.

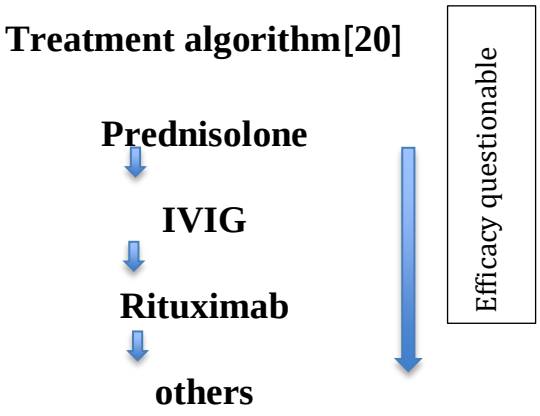
Immune-mediated necrotizing myopathy (IMNM)[17,18,19]

The 2016 ENMC-IMNM categorizes IMNM into three subgroups according to positive antibodies:

1. antisignal recognition particle (SRP) IMNM,
2. anti3-hydroxy-3-methylgluaryl-coenzyme A reductase (HMGCR),
3. seronegative IMNM

6. IMNM can affect people of wide age range

In children, the disease can be slowly progressed and mimic muscular dystrophy; the youngest age of onset in IMNM is 10 months old in a patient with anti-HMGCR positivity



Scheme 3.3.

Summary for this case:

The Idiopathic Inflammatory Myositis(IIM) represents a heterogenous group of disorders affecting muscle and causing significant disability.

Serological testing is increasingly used to classify IIM, but also provides important clinical clues to disease associations (malignancy, extra muscular features) and prognosis.

Prednisolone and rituximab remain the backbone of immunotherapy, but there are promising trials underway to investigate novel treatments for refractory disease *.

In the meantime, there is growing evidence for IVIG and rituximab for IMNM, and multi-modality therapy for patients with rapidly progressive MDA5 DM.

Investigation also continues into treatment for IBM, with promising trials ongoing

Case 4. Congenital myopathy case

Description of the case: 1 y 6 months old boy.

Chief complaint: generalized muscle weakness and hypotonia

Family history: no neuromuscular diseases. No consanguinity. The patient has a healthy brother

Developmental history: he showed visual pursuit at 3 months. Otherwise, no developmental milestone was achieved including head control

Physical examination (at 1y3m): H 60 cm, W 3460 g, head circumference 41,5 cm. Marked generalized muscle hypotonia, weakness, and atrophy. Facial muscle was also involved and high-arched palate is seen. All deep tendon reflexes are absent.

Laboratory data: CK 439 IU/L(normal :62-287), AST 58, ALT 28, LDH 385, lactate-8,3 (normal 3-17), pyruvate 0,40(normal 0,30-0,94)

EMG: myopathic change

Muscle CT: generalized atrophy

Brain MRI: T2- high signal in periventricular area.

History of the illness

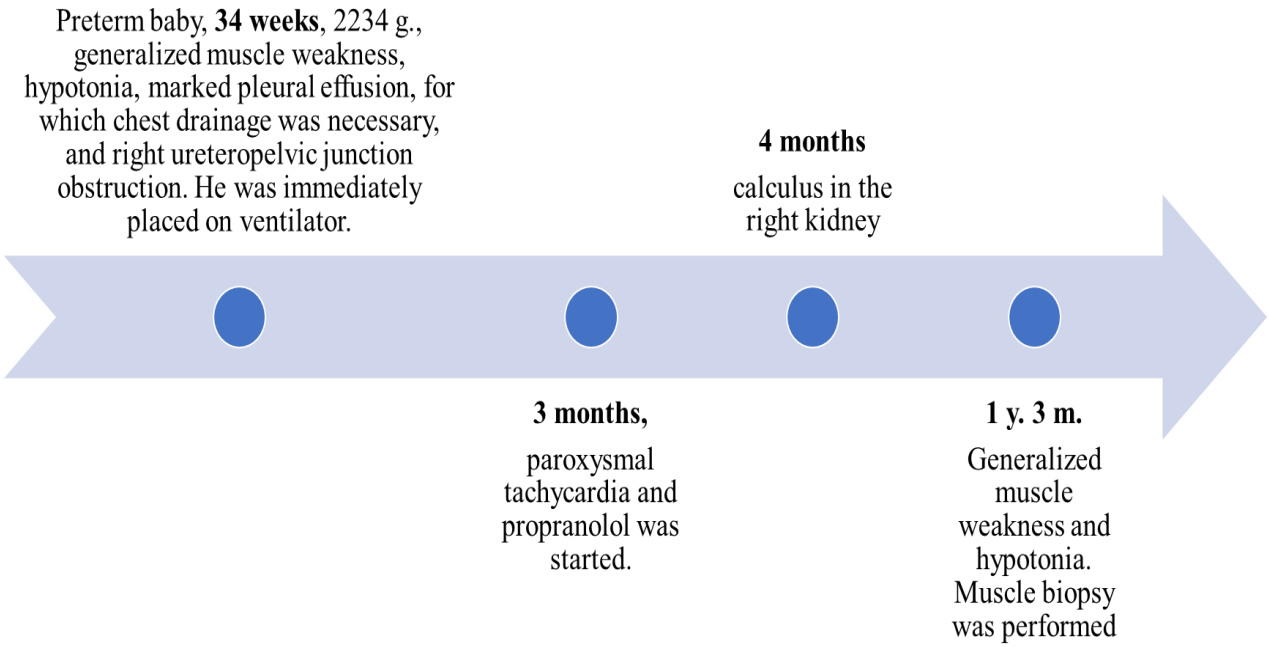


Table 4.1.

Clinical summary: key findings

Preterm child (was born at 34 weeks), normal birth weight, low Apgar score, hypotonia, muscle weakness, pleuritis, ureteropelvic obstruction, need in ventilation, no information about asphyxia.

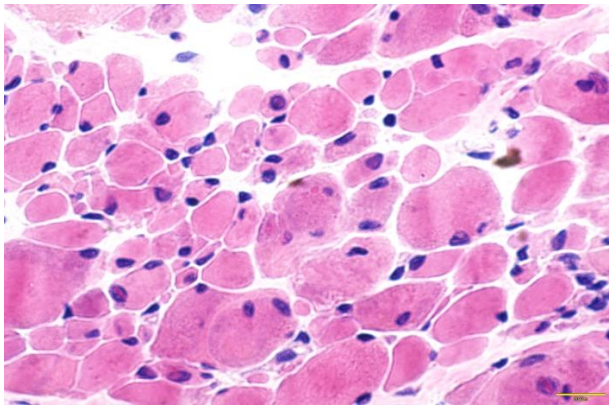
At the age of 1y 3 m. hypotrophy, microcephaly, developmental delay, facial muscles involvement, high-arched palate, DTR absent, failure to thrive

Differential diagnosis at first look

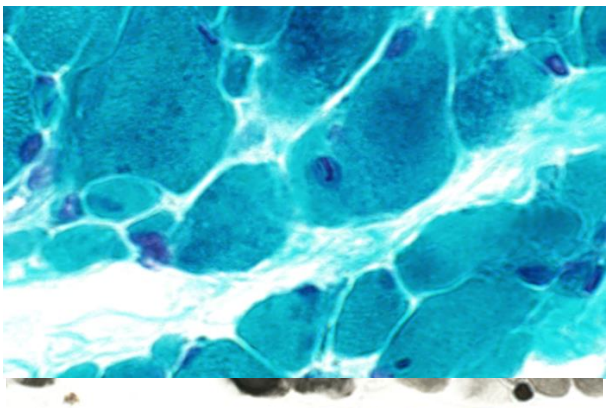
Condition	Prons	Cons
CP (cerebral palsy)	Low Apgar score, lung ventilation, developmental delay, CK slightly elevated, failure to thrive, T2- high signal in periventricular area.	Hypotonia, muscle weakness, pleuritis, ureteropelvic obstruction from the right side, no information on asphyxia, facial muscle weakness, high-arched palate, absent DTRs, EMG-myopathic changes
Myopathy	Normal body weight at birth, hypotonia, muscle weakness, need ventilation, at 3 month developed paroxysmal tachycardia, at 4 months developed calculus in the right kidney, failure to thrive, facial muscle weakness, high-arched palate, absent DTR, on EMG – myopathic changes, Muscle CT: generalized atrophy	No neuromuscular disease in family, no consanguinity, CK slightly elevated, microcephaly.

Table 4.2.

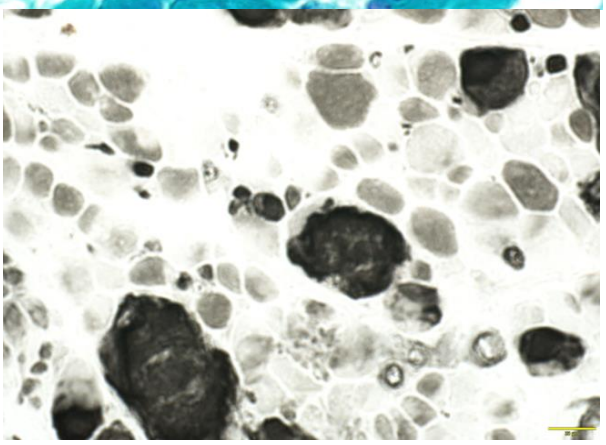
Muscle biopsy data (Pic.4)



Pic.4.1. H&E staining, fiber size variation is moderate, some fibers with enlarged and centrally-placed nuclei, some fibers with rods.



Pic.4.2. mGT: some fibers with centralized nuclei and rods



Pic.4.3. On ATPase, Type 1 fiber atrophy

Muscle biopsy findings

Myopathic changes:

1. Fiber size variation, moderate
2. Fibers with enlarged and centrally-placed nuclei, some
3. Fibers with intranuclear rods, some
4. Type 1 fibers atrophy

The above findings reflect to chronic myopathic condition. Together with the presence of intranuclear rods these findings are suggested of nemaline myopathy.

1. Generalized muscle weakness and hypotonia
2. Normal body weight at birth, early ventilation, at 3 months paroxysmal tachycardia, at 4 months calculus in right kidney. at 1 y 3 m failure to thrive, facial muscle involvement, high-arched palate, DTR absent.
3. CK was slightly elevated 439 IU/L (normal :62-287),
4. EMG: myopathic changes
5. Muscle CT: generalized atrophy
6. Muscle biopsy: Fibers with enlarged and centrally-placed nuclei and fibers with intranuclear rods, type 1 fiber atrophy.

All above compatible with myopathic condition. Nemaline myopathy is suspected. And finally, ACTA1 gene mutation detected

General considerations on congenital myopathies including ACTA1 myopathies [21,22].

A gene on chromosome 1q42.13 that encodes alpha actin 1, which is expres sed in skeletal muscle.
ACTA1 mutations cause nemaline myopathy type 3, congenital myopathy with e xcess of thin myofilaments, congenital myopathy with cores and congenital myo pathy with fibre-type disproportion.

It is a diverse group of clinically and histologically heterogeneous muscular disorders.

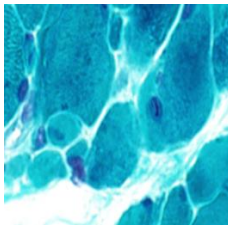
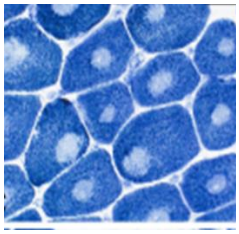
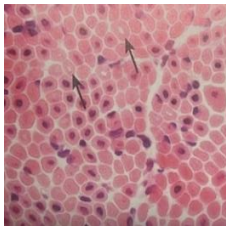
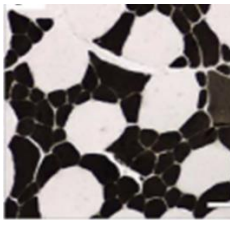
Commonly, the onset occurs in the neonatal period.

The diagnosis of CM should be based on a careful review of the clinical features and confirmed by additional investigations, with an exclusionary diagnosis of other myopathies.

Histopathological oriented classification is widely used for the diagnosis of CM, and recently tends to be replaced by genetic diagnosis in the era of modern genetics.

Histopathological types of congenital myopathies

Nemaline myopathy	**Core myopathy**	**Central nuclear**	**Congenital fiber type disproportion myopathy**
Presence of small rod-like inclusions in muscle fibers. These inclusions are clearly visualized by Gomori trichrome staining, which is mainly made up of alpha-actin and Z-band filaments.	Central core and multi-minicore myopathies, with histopathological features of focally reduced oxidative activity on muscle biopsy.	Numerous centrally placed or internalized nuclei with the absence of necrosis or excessive regeneration	Disproportionate difference in fiber caliber between type I and type II muscle fibers, in which type I muscle fibers are smaller than type II muscle fibers

The prevalence is 1 in 26 000 and CMs are the cause of 14% of all neonatal hypotonia cases*

The onset from birth to adulthood.

Slowly progressive or stable clinical course.

Normal intelligence and the central nervous system is not involved.

Early clinical signs: hypotonia (‘floppy infant syndrome’), muscle weakness, hypotrophy, and/or delayed motor milestones, facial weakness (myopathic face, ptosis and ophthalmoparesis) can be very pronounced, sometimes necessitating a feeding tube in the neonatal period and leading to a mouth held in an open position.

Facial deformities as an elongated face, micrognathia, or high-arched palate, and skeletal deformities, such as scoliosis, pectus excavatum, hip dislocation, or club feet, are also frequent. In case of prenatal onset, polyhydramnios, fetal akinesia, and arthrogryposis can be present[23,24,25].

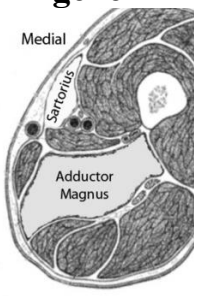
Specific clinical features of congenital myopathies and commonly associated genes

Table.4.3.

Clinical feature	Congenital myopathy/gene
Eye involvement	DNM2, MTM1, RYR1
Cardiac involvement	ACTA1, MYH7, TTN
Respiratory involvement out of proportion to skeletal muscle weakness	ACTA1, NEB, SEPN1, TPM3
Foot drop/pes cavus	DNM2, MYH7, NEB, TPM2, TPM3
Rigid spine	RYR1, SEPN1
Scoliosis	NM, RYR1, SEPN1
Severe facial weakness	CNM (DNM2, MTM1, RYR1), NM
Facial dysmorphism (elongated face, high arched palate, dolichocephaly)	CNM (severe DNM2, MTM1), NM, severe RYR1
Marked congenital hypotonia	MTM1, NM, RYR1
Early predominant axial hypotonia	RYR1, SEPN1
Early bulbar weakness (sucking, swallowing)	CNM (MTM1), NM, severe RYR1
Severe respiratory involvement at birth	CNM (MTM1), NM, severe RYR1
Malignant hyperthermia	RYR1, DNM2, dynamin 2; MTM1, myotubularin;

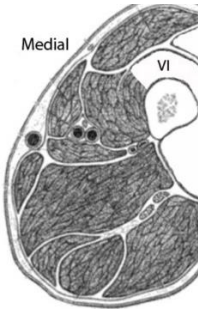
MRI of different Congenital Myopathies
[https://neuromuscular.wustl.edu]

Nemaline myopathy, ACTA1 gene

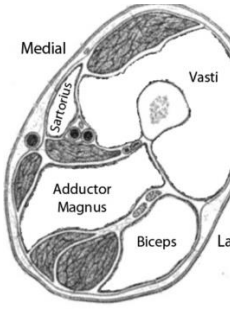


Rod myopathy, dominant (de novo) ACTA1 (Thr204Ile): Neck: Sternocleidomastoid Thigh: Sartorius>Adductors

Central core, RYR1

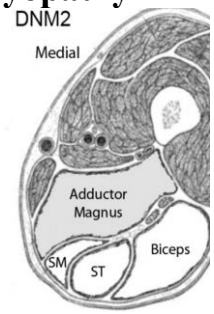


Rod myopathy, dominant, ACTA1(Gly50Ser): Neck: Sternocleidomastoid Thigh: Vastus intermedius & lateralis



Head: Masticatory Thigh:Anterior>Posterior, Vasti, Sartorius, Adductor magnus

Centronuclear myopathy



Trunk: paraspinous Thigh: posterior, adductor: Biceps: semimembranosus

Pic.4.4.

DIFFERENTIAL DIAGNOSES OF CONGENITAL MYOPATHIES
Table 4.4.

Congenital muscular dystrophies	Congenital myotonic dystrophy type 1	Metabolic myopathies including Pompe disease	Congenital myasthenic syndromes	Spinal muscular atrophy
Elevation of CK level more than five times upper normal value Muscle (pseudo)hypertrophy Extreme joint hyperlaxity (COL6)	Myotonia sign	Muscle (pseudo)hypertrophy should suggest a muscular dystrophy	Repetitive nerve stimulation and single-fiber electromyograph	Tongue fasciculations

NEED TO REMEMBER!!![25]

CMs AND MALIGNANT HYPERTHERMIA(MHT)

1. MHT is a medical emergency and defined by hyperthermia, muscle rigidity, and hypermetabolism as a result of using triggering anesthetic agents, particularly volatile gases and depolarizing muscle relaxants like succinylcholine.
2. MHT is treated with dantrolene, which antagonizes the intracellular release of calcium by the ryanodine receptor 1, and additional supportive care measures.
3. MHT is suspected in an individual with CMs, if:
    1. there is a positive family history of MHS;
    2. there have been previous problems with anesthesia;
    3. the patient has a proven RYR1 mutation.

Summary on congenital myopathies

The clinical features, muscle biopsy, muscle imaging, and genetic analyses are essential in the diagnosis of CMs.

Management is performed by a multidisciplinary team specialized in neuromuscular disorders, where the pediatric neurologist has an essential role.

To date, only supportive treatment is available, but novel pathomechanisms are being discovered and gene therapies are being explored.

Case 5. Dermatomyositis case

Description of the case of 67 y. o, man

Chief complaints: muscle weakness and pain

Past medical history: negative

Family history: no neuromuscular disease

Physical examination: marked, predominantly proximal muscle weakness, spearing facial muscles. Mild dysphagia. Muscle atrophy also seen in proximal limb and trunk muscles. Muscles tenderness was present in QF, deltoid and BB muscles. Calf muscle hypertrophy was not seen. Gowers' sign was positive. DTRs were absent. Skin rash, including heliotrope rash, Gottron papule and mechanic's hand, was not seen.

Laboratory data: CK 118 IU/L(normal 26-287), Autoantibodies: Jo-1(-), ANA 320 x speckled

EMG: early recruitment, fibrillation, low polyphasic units

ECG: normal

Chest Xray: no interstitial pneumonia

History of the illness

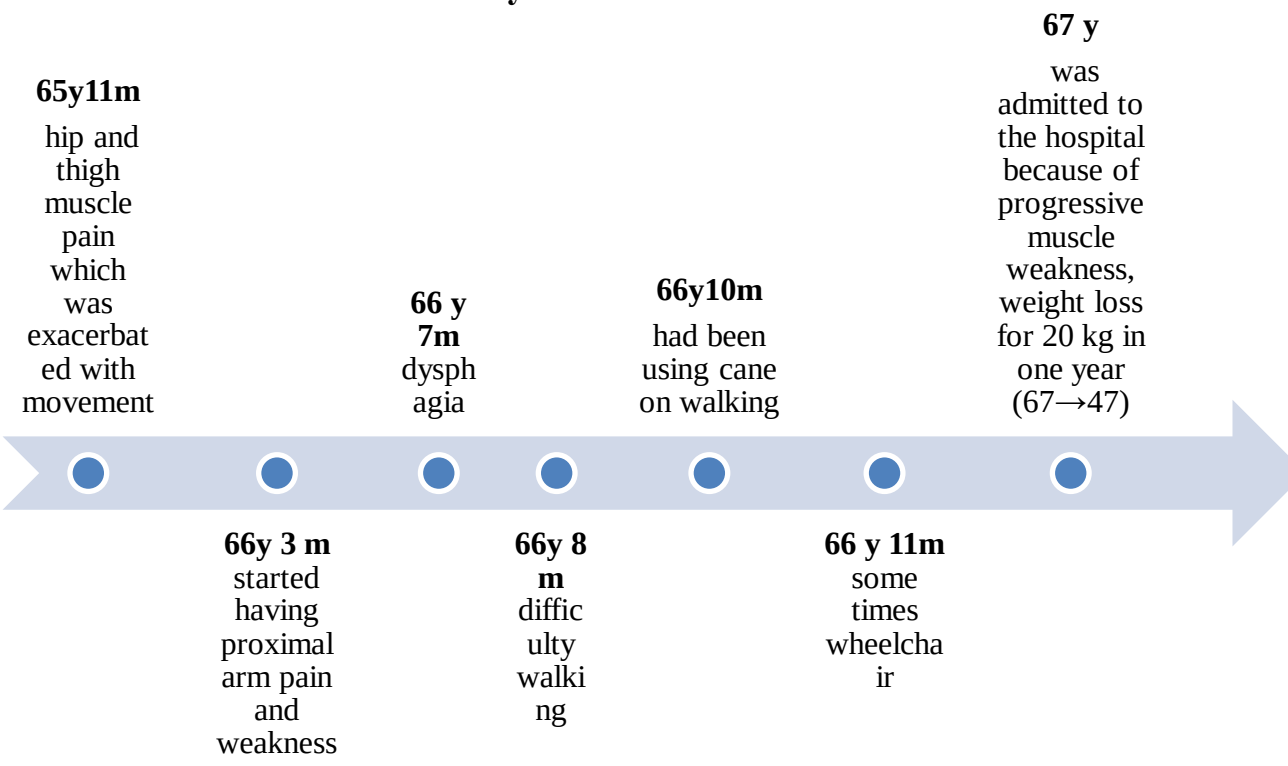
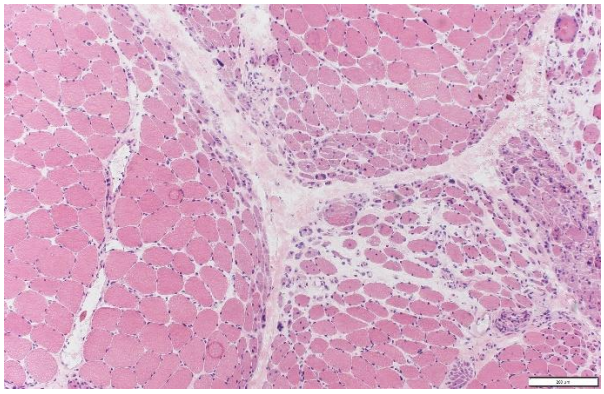


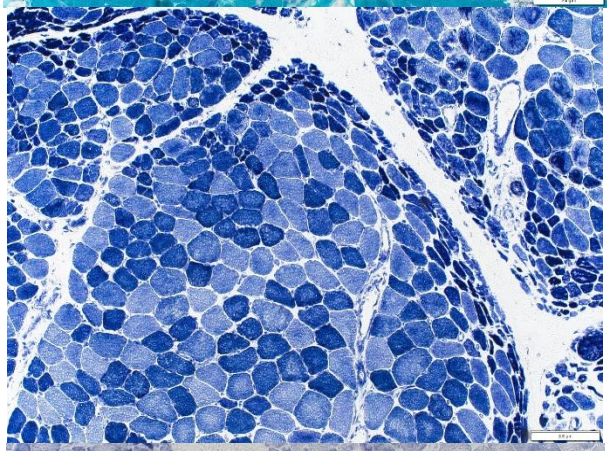
Table 5.1.

Muscle biopsy data (Pic.5)

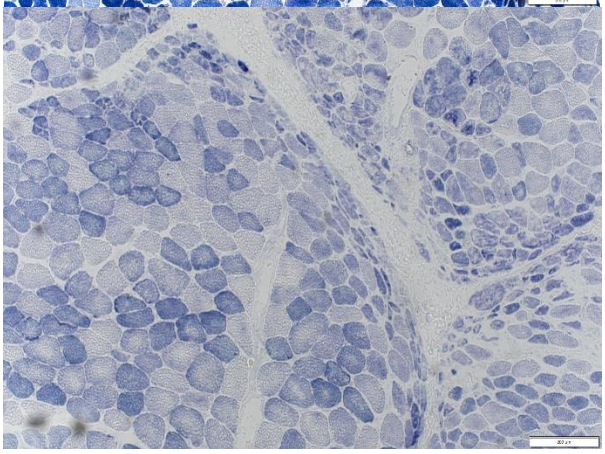


Pic.5.1. On H&E: there is marked fiber size variation measuring from 10 to 120 microns in diameter. There are fibers with internal nuclei. Mild or moderate endomysial fibrosis is seen. Perifascicular atrophy of fibers is seen (blue arrows). Punched-out vacuoles in several fibers are seen

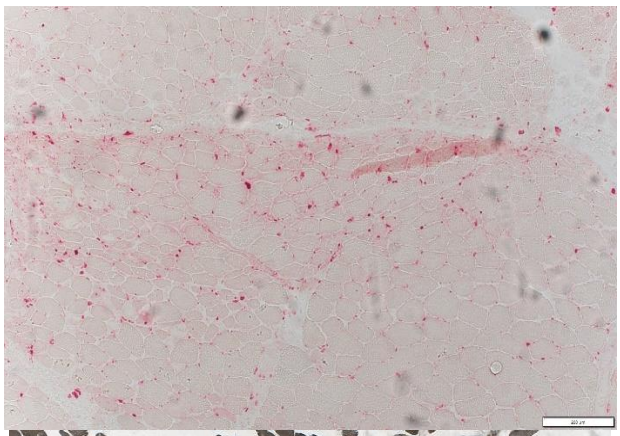
Pic.5.2. On mGT, ragged-red fibers (RRFs), nemaline rods, rimmed vacuoles are not seen. Peripheral nerve is not included in the present biopsy



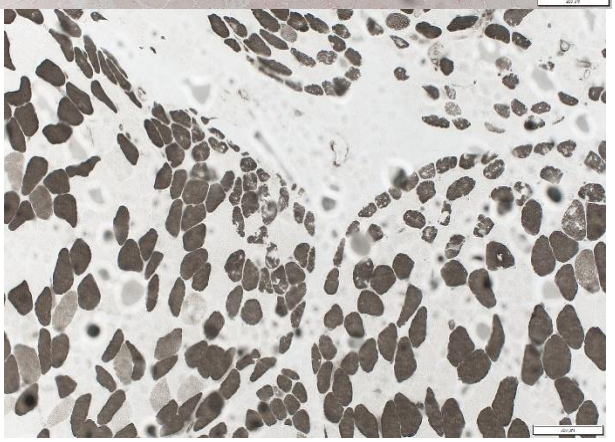
Pic.5.3. On NADH-TR, intermyofibrillar networks are markedly disorganized in perifascicular area



Pic.5.4. On SDH, the strongly SDH-reactive blood vessels (SSVs) are not highlighted

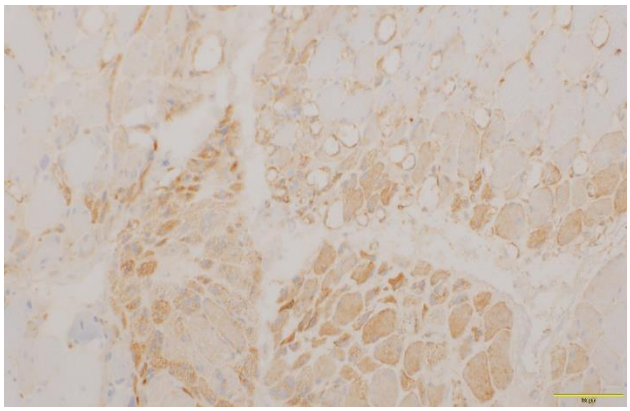


Pic.5.5. Acid phosphatase activity (blue arrow) in several fibers including in the perifascicular region.



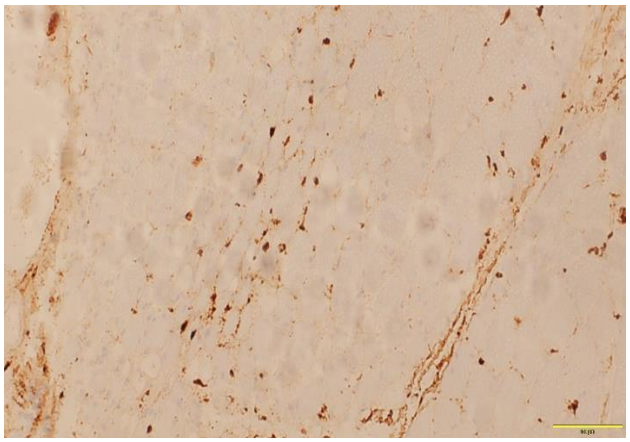
Pic.5.6. On ATPase, Type 1, 2A, 2B, and 2C fibers comprise 40%, 40%, 15%, and 5%. Type 1 and type 2 fiber atrophy is seen

Immunohistochemistry



Pic.5.7. On MxA*: in perifascicular area expression of MxA (type 1 interferon)

*-Myxovirus resistant protein A is a marker for type 1 interferon production



Pic.5.8. On MAC: capillary deposition is seen

Myopathic changes with:

1) Variation in fiber size, marked
2) Necrotic and regeneration fibers, a few
3) Perifascicular atrophy
4) Type 1 and type 2 fiber atrophy5) Type 2C fibers, some

The above findings are suggestive of chronic condition, small fibers restricted to perifascicular areas suggested to dermatomyositis. Final diagnosis is pending on IHC.

Together with IHC findings (perifascicular area expression of MxA and capillary deposition on MAC) compatible with dermatomyositis.

Literature Overview on dermatomyositis[21]

1. Dermatomyositis is a disease from the large and heterogenous group of acquired disorders that have been grouped together collectively as inflammatory myopathies
2. It is a quite important disorder for pediatric practice.
3. Recognizing the form of inflammatory myopathy is important as many respond well to drug therapy.
4. Therapy regimes, however are variable and although the use of corticoids common and beneficial in number of situations, side-effects have to be monitored and not all cases are responsive (for example, patients with IBM frequently show no response to corticosteroids, but IBM it is an adult disorder).

Autoantibodies specific for clinical presentations:

1. DM without skin rush: Mi-2, MDA5, SAE, NxP-2, CADM
2. Pulmonary failure: MDAS, Mi-2, Tif1ɣ
3. Malignancy: Tif1ɣ

Key findings from the case

1. Progressive muscle weakness and pain
2. Rush
3. Dysphagia
4. Positive ANA
5. EMG: early recruitment, fibrillation, low polyphasic units

Muscle biopsy and IHC: perifascicular atrophy together with perifascicular area expression of MxA and capillary deposition on MAC are compatible with dermatomyositis.

The condition could be curable with steroid therapy!!!!

Differential diagnosis [21]

	Dermatomyositis	Muscular dystrophies
Onset	Acquired, acute condition	Inherited, chronic
Age of onset	childhood to adulthood, even after 60	Childhood and middle adulthood
Muscle involvement	Have varying distribution	Selective muscles according to the specific muscle dystrophies
Muscle weakness	Acute, proximal, varying distribution, rapidly progressive, accompanied by muscle pain	Mainly symmetrical, selective muscles, chronic, gradual deterioration, no pain.
CK level	Elevated, no more then 5000	Elevated, often more the 5 000
Association with malignancy	Yes	No
Skin changes	Yes (heliotrope or violaceous rash, particularly over the eyes, malar region of face, erythema around the nail beds, over knees and elbows, in juvenile cases calcinosis)	No
Serum antibodies	Positive	Negative
Muscle MRI	Oedema and inflammatory changes in subcutaneous fat. The changes not specific.	Specific involvement of muscles with fat infiltration.
Treatment	Majority of cases respond to steroid therapy	No curable (symptomatic treatment in some cases)

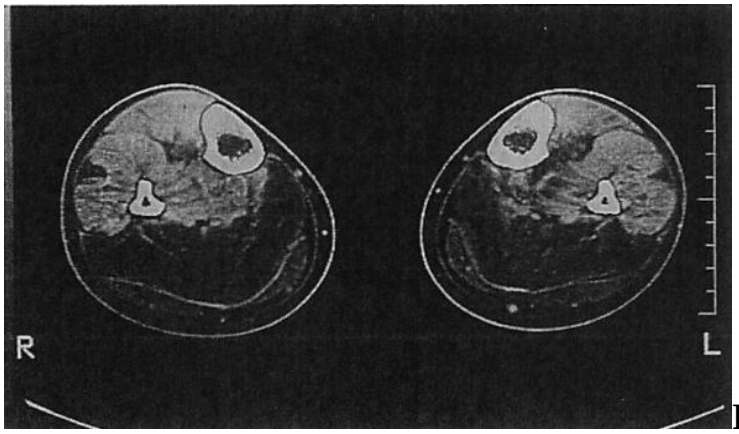
6. Age of onset: after 65 y
7.

Table 5.2.

Case 6. Dysferlinopathy

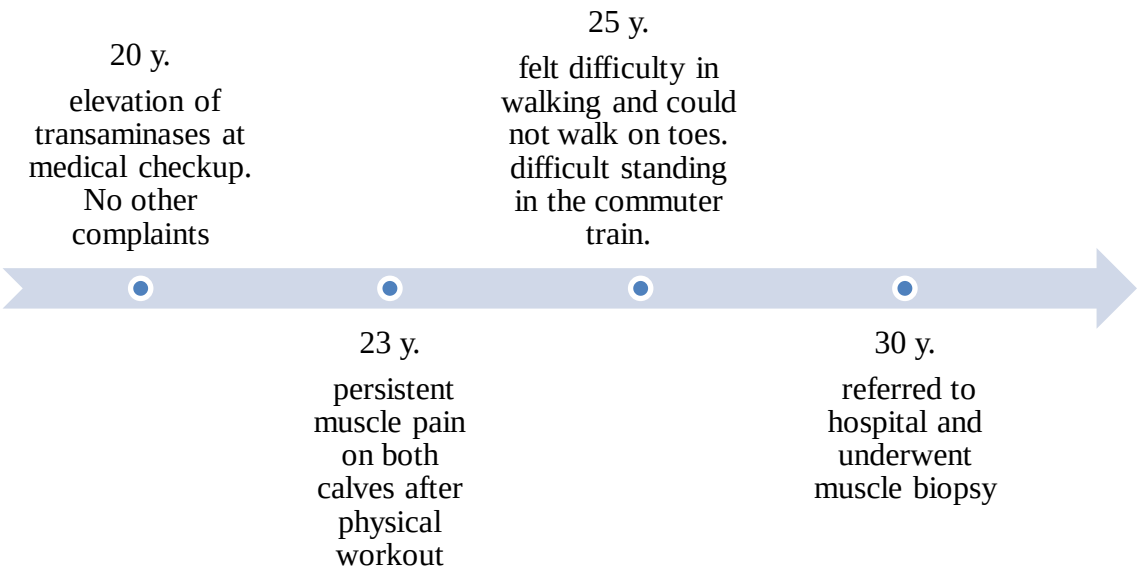
Description of the case of 30 y, man

1. Chief complaint: gait disturbance
2. Past medical history: noncontributory
3. Family history: no neuromuscular disease, no consanguinity
4. Physical examination: he had mild distal leg weakness. He could not stand or walk on toes. His calf muscles were atrophic. Proximal muscles showed minimal weakness. No finger muscle weakness was seen. He had no facial muscle involvement. Achilles tendon reflexes were decreased.
5. Laboratory data: CK: 4800 IU/L (normal <189)
6. Muscle CT: fatty change in calf muscle

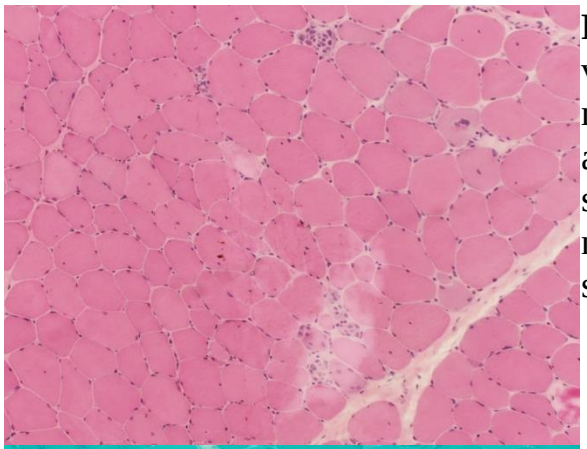


Pic.6.1.

History of illness

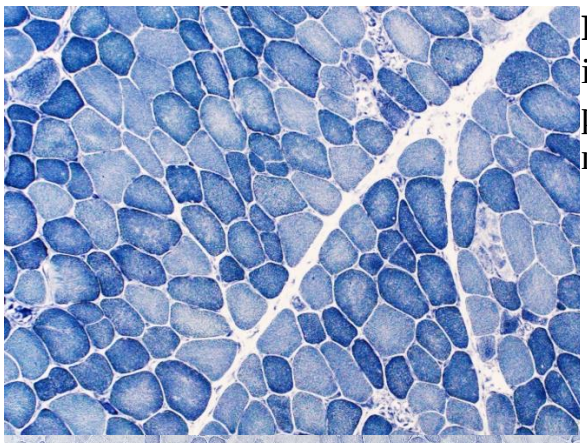


Muscle biopsy data

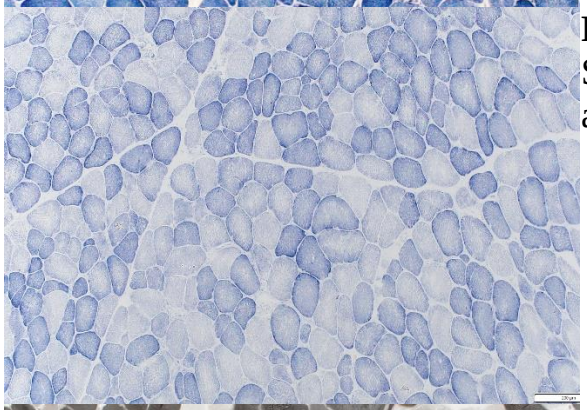


Pic.6.2. On H&E: there is moderate variation in fiber size from 20 to 80 microns in diameter. A few necrotic and some regenerating fibers are seen. Some fibers have internal nuclei. mild endomysial fibrosis is seen

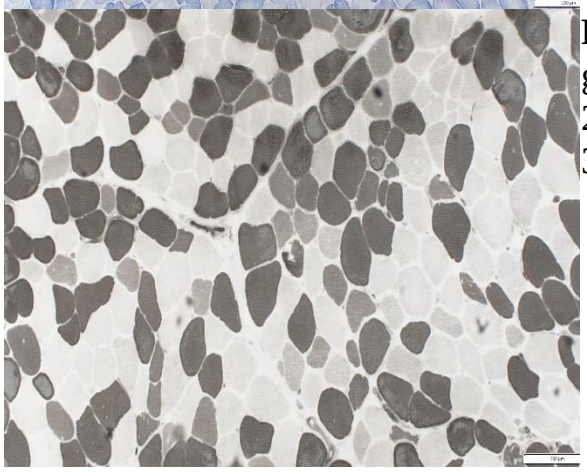
Pic.6.3. On mGT, ragged-red fibers (RRFs), nemaline rods and rimmed vacuoles are not seen. Peripheral nerve is not included in the present biopsy



Pic.6.4. On NADH-TR, intermyofibrillar networks are present well escape of some necrotizing fibers

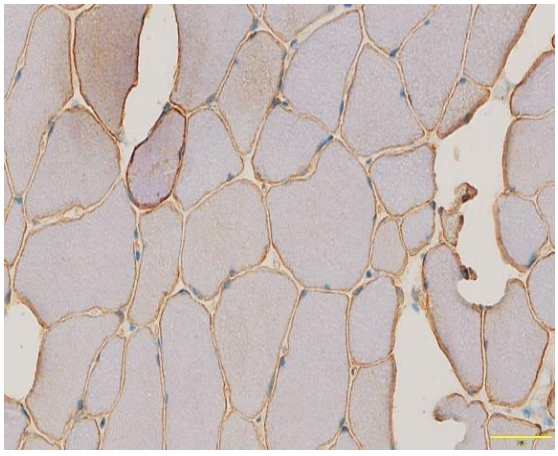


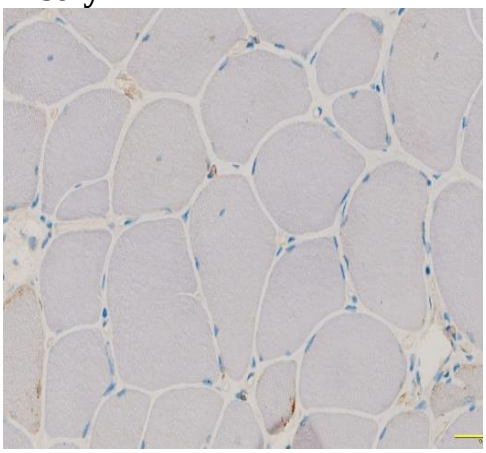
Pic.6.5. On SDH, there strongly SDH-reactive blood vessels (SSVs) are not highlighted



Pic.6.6. On ATPase, fiber type grouping is not seen. Type 1, 2A, 2B, and 2C fibers comprise 40%, 35%, 15%, and 5%

Immunohistochemistry





Normal expression of dysferlin **Absence of dysferlin expression in our case**

Pic.6.7.

Myopathic change with:

1. Variation in fiber size, moderate
2. Necrotic and regenerating fibers, a few respectively
3. Type 2C fibers, some

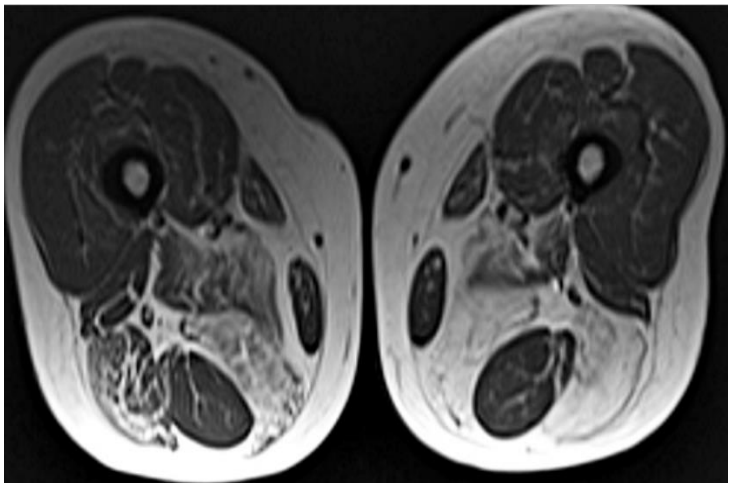
The above finding is suggestive of chronic mild muscular dystrophy.

Final diagnosis is pending on IHC.

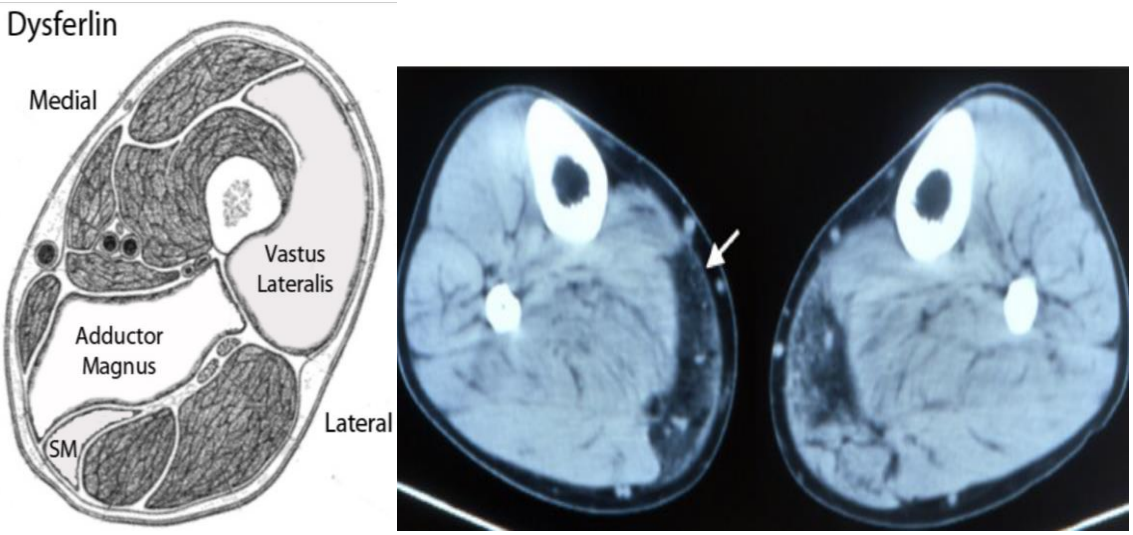
Together with the results of IHC these findings are compatible with dyspherlinopathy.

On MRI calf muscles are absent which is also compatible with disferlinopathy.

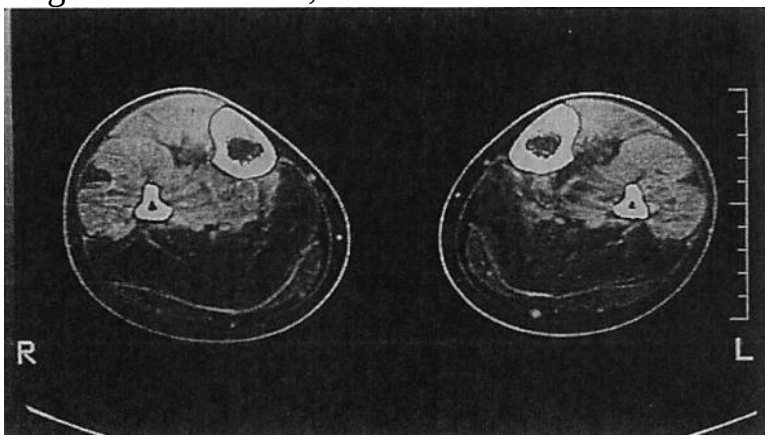
Imiging data [https://neuromuscular.wustl.edu]



Pic.6.8.



Refferal MRI findings:
Arms: forearm flexor
Pelvis: gluteus minimus
Thigh: Adductors: Vasti; semimembranosus
Leg: Gastrocnemius, medial



Pic.6.9.

CT of muscles of our case.

Key findings of this case:

1. 30 y, man
2. Chief complaint: gait disturbance
3. Physical examination: mild distal leg weakness, could not stand or walk on toes, calf muscles atrophy. Minimal proximal muscles weakness. No finger muscle weakness or facial muscle involvement. Achilles tendon reflexes decreased.
4. CK: elevated 4800 IU/L (normal <189)
5. Muscle CT: fatty change in calf muscle
6. Muscle biopsy and IHC: chronic myopathic condition, no dysferline expression.

All above findings compatible with - dysferlinopathy (LGMD2B)

An overview on dysferlinopathy [26]

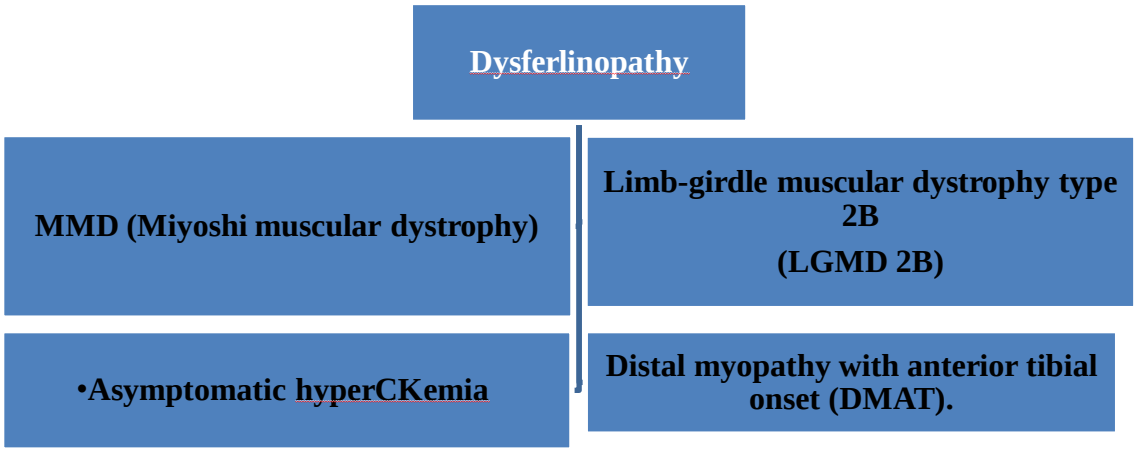


Table 6.1.

The diagnosis of dysferlinopathy is established in a proband with suggestive findings and biallelic pathogenic variants in *DYSF* identified by molecular genetic testing.

Major Phenotypes[Izumi et al 2020]	
Miyoshi muscular dystrophy (MMD)	**Limb-girdle muscular dystrophy 2B (LGMD2B)**
•Mid- to late-childhood or early-adult onset; mean age at onset 19.0 years •Early and predominant distal muscle weakness affecting the upper and lower limbs, particularly the calf muscles (i.e., gastrocnemius and soleus muscles) •Slow progression •Elevation of serum CK concentration, often 10-100 times normal; mean CK: 8,940 IU/L •Primarily myogenic pattern on EMG	•Predominant early weakness and atrophy of the pelvic and shoulder girdle muscles •Onset in the proximal lower-limb muscles in the late teens or later •Slow progression •Massive elevation of serum CK concentration •Subclinical involvement of distal muscles, identified by careful examination or ancillary investigations such as muscle CT scan and MRI

Table 6.2.

Minor phenotypes

Asymptomatic hyperCKemia

characterized by marked elevation of serum CK concentration only

Distal myopathy with anterior tibial onset (DMAT)

characterized by early and predominant distal muscle weakness affecting the lower limbs, particularly the muscles of the anterior compartment of the legs.

Comparison of phenotypes by selected features[26]

Feature	MMD	LGMD2B	Feature	MMD
Percent	49.8%[1]	39.2%[1]	**Percent**	49.8%[1]
Mean age at onset (range)	22.1 yrs[1] (10-48)	28.2 yrs[1] (10-63)	**Mean age at onset (range)**	22.1 yrs[1] (10-48)
Average age when use of a cane is required (yrs after onset)	35.5 yrs[2] (16 yrs)	39.3 yrs[2] (13.6 yrs)	**Average age when use of a cane is required (yrs after onset)**	35.5 yrs[2] (16 yrs)
Age when wheelchair bound (yrs after onset)	42.8 yrs[2] (22.8 yrs)	45.1 yrs[2] (21.4 yrs)	**Age when wheelchair bound (yrs after onset)**	42.8 yrs[2] (22.8 yrs)

Median CK level	4,440 [1]	3,481 [1]	**Median CK level**	4,440 [1]
Cardiac complications	3.6% [3]		**Cardiac complications**	3.6% [3]
Respiratory complications	22.8% [3]		**Respiratory complications**	22.8% [3]

Table 6.3.

Differential diagnosis

1. Other LGMD – gene panel could help to distinguish
2. Distal myopathies (table below)
3. Dystrophinopathies (DMD/BMD)- yearly age, mutation in DMD gene, CK level is very high

Distal myopathy[26]

Gene	Disorders	MOI	Mean Age at Onset (Yrs)	Initial Muscle Group Involved	Serum Creatine Kinase Concentration	Muscle Biopsy
GNE	*GNE* myopathy (Nonaka distal myopathy)	AR	20-40	Anterior compartment in legs	Normal or ↑; typically ≤4x normal	Rimmed vacuoles
LDB3 (*ZASP*)	Myofibrillar myopathy 4 (OMIM 609452)	AD	>40	Anterior compartment in legs	Normal or slightly ↑	Vacuolar & myofibrillar myopathy
MATR3	Amyotrophic lateral sclerosis 21 (formerly MPD2) (See ALS Overview.)	AD	35-60	Asymmetric lower leg & hands; dysphonia	1-8x normal	Rimmed vacuoles
MYH7	Laing distal myopathy	AD	<5	Ankle & great toe extensors	Usually normal; rarely 8x normal	Type I fiber atrophy in tibial anterior muscles; disproportion in proximal muscles
MYOT	Myofibrillar myopathy 3 (OMIM 609200)	AD	>40	Posterior > anterior in legs	Slightly ↑	Vacuolar & myofibrillar myopathy
TIA1	Welander distal myopathy (OMIM 604454)	AD AR	>40	Intrinsic muscles of hand & extensor pollicus longus	Normal	Rimmed vacuoles
TTN	Udd distal myopathy – tibial muscular dystrophy	AD	>30	Anterior compartment in legs	Normal or slightly ↑	± Rimmed vacuoles

Table 6.4.

Management

Treatment of manifestations: There is no approved therapy for dysferlinopathy. Treatment is symptomatic only. Management should be tailored to the individual and the specific subtype. Individualized management may include physical therapy, use of mechanical aids, surgical intervention for orthopedic complications, respiratory aids, and social and emotional support.

Surveillance: Annual monitoring of muscle strength, physical function, activities of daily living, joint range of motion, balance, and respiratory function, and for evidence of cardiomyopathy for individuals with cardiac involvement.

Agents/circumstances to avoid: Weight control to avoid obesity

Case 7. Floppy baby case

Description of case of 1y 4 month, boy.

The patient is the second child of healthy and non-consanguineous parents. He was born via normal spontaneous delivery. No problems were encountered during perinatal and neonatal periods. At the age of 7 months, he was noticed to be floppy, with poor head control and with minimal spontaneous movements. This condition persisted; he was later admitted to the hospital for work up at 15 months of age.

He had delayed development milestones: head control at the age of 6 months and able to roll over at 1 year.

At present he could not sit independently, speak a meaningful word.
On neurological examination, he had generalized hypotonia with a frog-leg posture and an inverted U sing. Spontaneous movements were visible albeit weak. He had no calf muscle hypertrophy or joint contractures. DTR were decreased. No cerebellar signs were elicited. Careful ophthalmologic examination showed no abnormality.

CK- 137 IU/l(normal 12-79), lactate and pyruvate is normal;
Muscle CT: generalized muscle atrophy; brain MRI: cerebellar atrophy

Suspected conditions at first look

	prons	cons
SMA	Floppy, generalized hypotonia, poor head control, minimal spontaneous movements, DTR decreased CT generalized muscle atrophy	Slow development Cerebellar atrophy
Congenital myopathy	Floppy, hypotonia, poor head control, no calf muscle hypertrophy, DTR decreased, CK 137 IU/l(normal 12-79)	No joint contracture, MRI: cerebellar atrophy, CT generalized muscle atrophy
Congenital myasthenic syndrome	No muscle weakness, only hypotonia	Was normal until 7 months of age

Table 7.1.

Differential diagnosis[27]

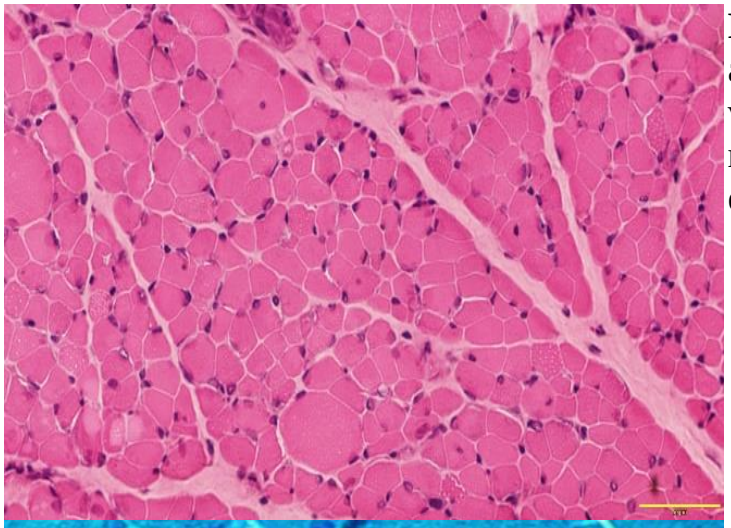
Disease	Diagnosis Similarities	Differences	Diagnostic test
Spinal Muscular Atrophy	Floppy infant or child with muscle weakness. Respiratory and bulbar involvement. Contractures (SMA1)	Absence of ptosis, and facial weakness. Absent deep tendon reflexes. Presence of tongue fasciculation, polyminimyoclonus	SMA genetics
Congenital Myotonic Dystrophy	Floppy infant or child with muscle weakness. Respiratory and bulbar involvement. Contractures. Ptosis and Facial weakness	Mother affected with Myotonic Dystrophy (may be undiagnosed) EMG - no decrement on RNS or abnormal jitter/block	Myotonic Dystrophy genetics
Congenital Myopathy/ Muscular Dystrophy	Floppy infant or child with muscle weakness Respiratory and bulbar involvement Contractures Facial weakness May have ptosis	Characteristic Muscle biopsy abnormalities EMG - no decrement on RNS or abnormal jitter/block	Muscle Biopsy Muscle MRI Genetics
Mitochondrial Myopathy	Floppy infant or child with muscle weakness Respiratory and bulbar involvement Contractures Ptosis and facial weakness	May have other system involvement EMG - no decrement on RNS or abnormal jitter/block	Muscle Biopsy Genetics

Myasthenia Gravis	Fatiguable muscle weakness Respiratory and bulbar involvement Ptosis and facial weakness EMG - decrement on RNS or abnormal jitter/block	Age of onset (rare before 12 months). Absence of family history Absence of ankle-dorsiflexion weakness Ptosis can be asymmetric	Antibody (RIA and Cell based assay if available) AChR, MUSK and LRP4
Neonatal Myasthenia Gravis	Floppy neonate with muscle weakness Respiratory and bulbar involvement Ptosis and facial weakness EMG - decrement on RNS or abnormal jitter/block	Mother with Myasthenia gravis (May be undiagnosed)	Antibody testing of the mother
Limb Girdle Muscular dystrophy	Proximal Muscle weakness. Respiratory involvement Positive family history	EMG - no decrement on RNS or abnormal jitter/block	Muscle Biopsy Muscle MRI Genetics
Chronic Fatigue Syndrome	History of fatigability with gross motor and fine motor activities Clear period of prior normal motor function prior to onset of symptoms	Absence of: Muscle weakness of formal assessment; ptosis or facial weakness; EMG abnormalities	Clinical Diagnosis
Hypermobility Syndromes	History of 'fatigability' with gross motor and	Absence of: Muscle weakness on formal assessment; Ptosis or facial	Clinical Diagnosis

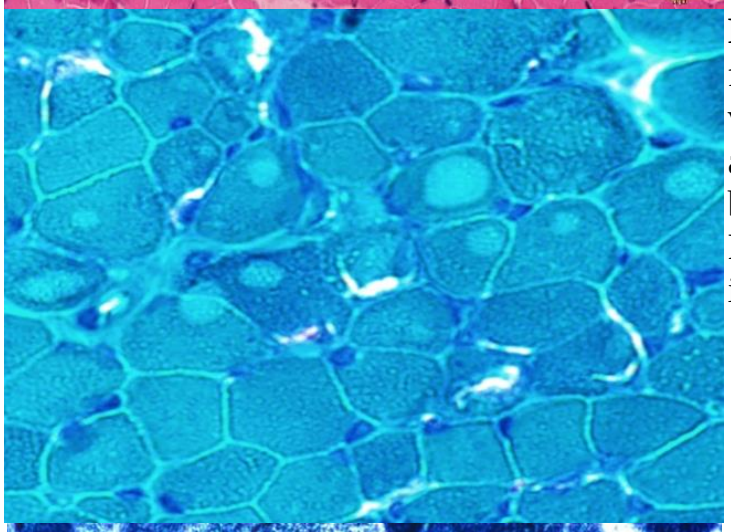
	fine motor activities	weakness; EMG abnormalities	

Table 7.2.

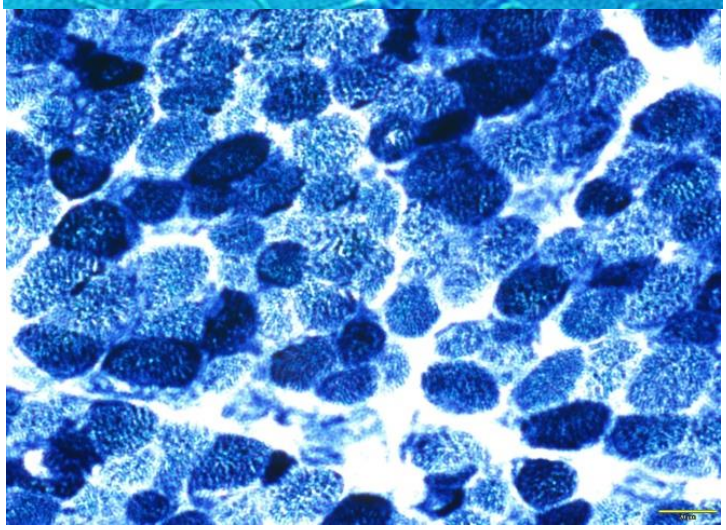
Muscle biopsy findings (Pic.7)



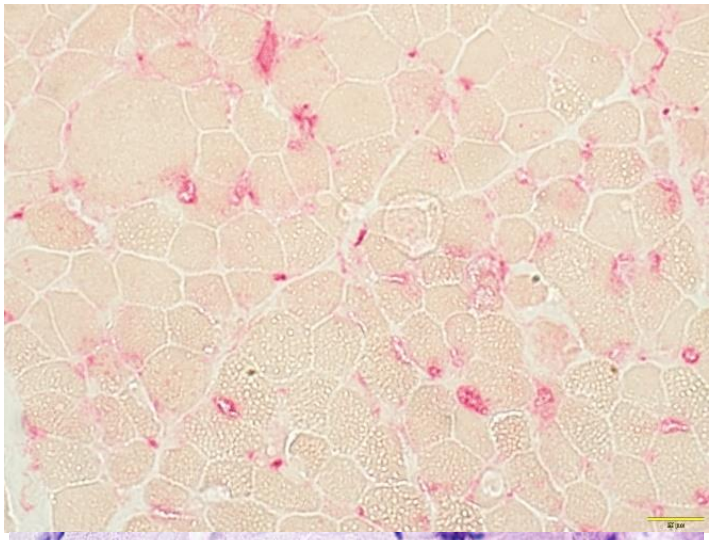
Pic.7.1. On H&E: there is a mild fibers size variation. No necrotic and regenerating fibers. A few endomysial fibrosis is seen



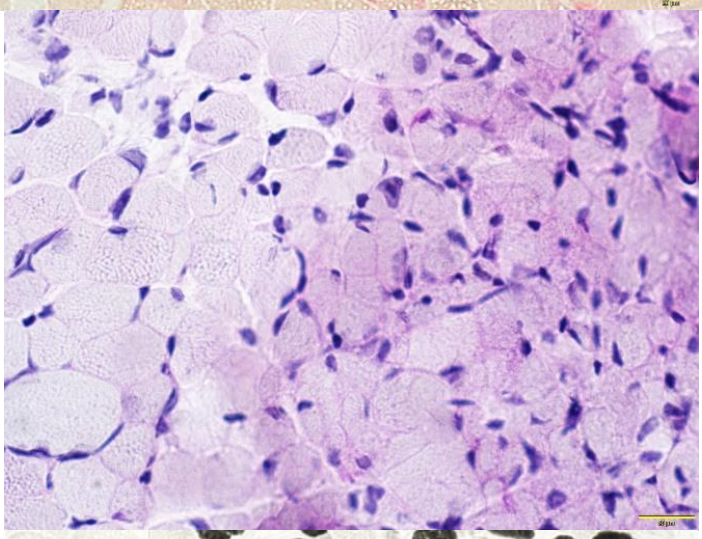
Pic.7.2. On mGT: some fibers with rimmed vacuoles* are seen(red arrows). No nemaline bodies and RRFs are seen . Peripheral nerve is not included to this section.



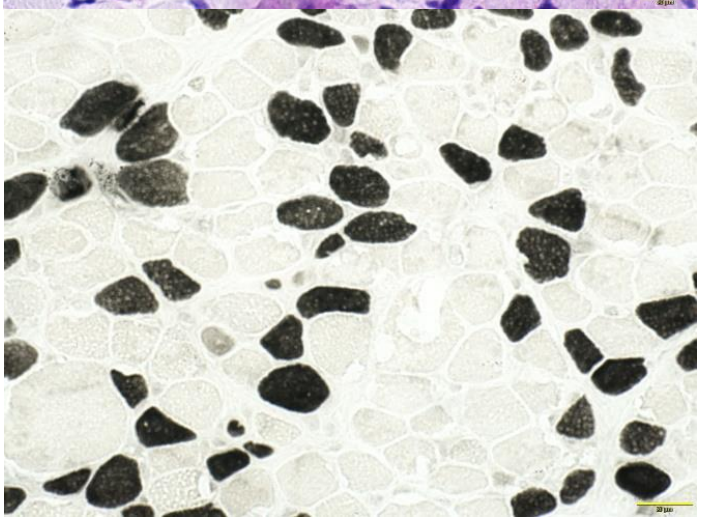
Pic.7.3. On NADH , intermyofibrillar network are disorganized in some fibers



Pic.7.4. On ACID, rimmed fibers has a red membrane*



Pic.7.5. On PAS*, no glycogen concentration in fibers.



Pic.7.6. On ATPase, there are type1 fiber atrophy* is seen, some type 2c fibers are seen, fiber type grouping

* Remarks regarding fiber atrophy

Selective type 1 atrophy occurs in several congenital myopathies and myotonic dystrophy. Type-specific hypertrophy is much less frequent but type 2 hypertrophy can occur in association with type 1 atrophy in congenital myopathies. However, the grouping hypertrophic fibers in spinal muscular atrophy are frequently type 1. the hypertrophy of fibers and the enlargement of

type 2 fibers may account for the normal difference between male muscle (in which type 2 fibers are larger than type 1) and female muscle (in which they are roughly equal in size)

*Vacuoles can occur in several conditions and they are of different types. The situation where they are most common are inclusion body myositis, myofibrillar myopathies, distal myopathies, glycogenosis and periodic paralysis, although absence of vacuoles in a sample does not exclude these diagnoses. Vacuoles are lined by membrane and two X-linked conditions are characterized by excessive autophagic vacuoles, one linked to Xq28(Kalimo et al, 1988) and the other caused by mutations in the LAMP2gene, also on the X chromosome (Nishino et al,2000).

Vacuoles may have basophilic granularity associated with them, particularly at the periphery. This type of rimmed vacuole is typical of inclusion body myositis and several other disorders including distal myopathies and myofibrillar myopathies. In glycogen storage disease routine stains show a vacuolar appearance where glycogen has accumulated (type V McArdle disease, Pompe disease)[21]

Conclusion according to biopsy data:

1.Fibers size variation, mild

2. Fibers with rimmed vacuoles, some

3. Endomysial fibrosis, mild

Above findings reflect to chronic myopathic changes. Final diagnosis is pending on gene analysis

SIL1 gene mutation was found!

Main consideration of the case:

1. Child, 1y.4m.
2. Developmental delay: head control at the age of 6 months and able to roll over at 1 year, could not sit independently, speak a meaningful word.
3. Neurological examination: generalized hypotonia with a frog-leg posture and an inverted U sing. Spontaneous movements are weak. DTR are decreased.
4. CK 137 IU/l(normal 12-79);
5. Muscle CT: generalized muscle atrophy; brain MRI: cerebellar atrophy
6. Muscle biopsy: chronic myopathic changes(mild fibers size variation; some fibers with rimmed vacuoles; mild endomysial fibrosis, type 1 fiber atrophy)
7. SIL1 gene mutation

Marinesco-Sjogren syndrome

Literature review [27]

1. Marinesco-Sjogren syndrome (MIM 248800) is a long-recognized autosomal recessively inherited, infantile-onset multisystem disorder that affects brain, eyes and skeletal muscles.
2. The clinical triad of bilateral cataracts, ataxia and intellectual disability was noted (Moravcsik, 1904; Marinesco et al., 1931; Sjogren, 1947).
3. Pathoanatomical and brain imaging studies revealed cerebellar atrophy (Todorov, 1965; Georgy et al., 1998).
4. Hypergonadotropic hypogonadism, skeletal abnormalities and short stature are additional features (Berg and Skre, 1976; Brogdon et al., 1996).
5. Although most patients are severely handicapped, life span in Marinesco-Sjogren syndrome is at least not drastically reduced (Anttonen et al., 2005).

Diagnosis/testing

Diagnosis is established in an individual with typical clinical findings and/or biallelic pathogenic variants of *SIL1* identified on molecular genetic testing**.

Electron-microscopic ultrastructural changes on muscle biopsy are thought to be specific to MSS*.

Management

Treatment of manifestations: **Symptomatic treatment** of muscular manifestations usually by pediatric or adult neurologists and physiatrists and/or physical therapists; education programs tailored to the individual's developmental needs; cataract extraction as needed; hormone replacement therapy for primary gonadal failure at the expected time of puberty.

Surveillance: Regular follow up with a child or adult neurologist and physiatrist and/or physical therapist; ophthalmologic examination at regular intervals beginning in infancy.

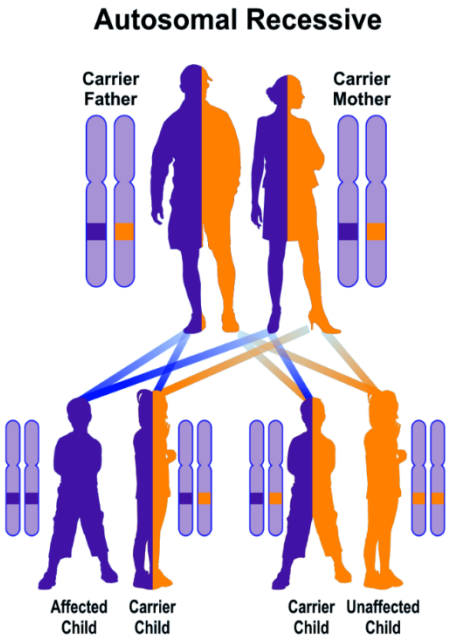
Genetic counseling

Marinesco-Sjögren syndrome (MSS) is inherited in an autosomal recessive manner.

The parents of an affected child are obligate heterozygotes and therefore carry one pathogenic variant.

At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.

Carrier testing for at-risk relatives and prenatal and preimplantation genetic testing are possible if the pathogenic variants in the family are known.



Pic.7.7.

Diagnosis

Suggestive Findings

Marinesco-Sjögren syndrome (MSS) **should be suspected** in individuals with the following clinical findings:

1. Cerebellar ataxia with cerebellar atrophy, dysarthria, and nystagmus
2. **MRI.** Cerebellar atrophy, usually more pronounced in the vermis than the hemispheres
3. Early-onset (not necessarily congenital) cataracts
4. Myopathy, muscle weakness, and hypotonia
5. **Serum CK concentration.** Normal or moderately increased (usually 2-4x upper-normal limits)
6. **EMG.** Myopathic features only
7. **Muscle biopsy**

Light microscopy. Variation in muscle fiber size, atrophic fibers, fatty replacement, and rimmed vacuole formation on light microscopy

Electron microscopy. Autophagic vacuoles, membranous whorls, and electron-dense double-membrane structures associated with nuclei (a specific ultrastructural feature of MSS) [Krieger et al,2013]

Additional features:

1. Psychomotor delay
2. Hypergonadotropic hypogonadism (i.e., primary gonadal failure)
3. Short stature
4. Various skeletal abnormalities including scoliosis; shortening of metacarpals, metatarsals, and phalanges; coxa valga; pes planovalgus; and pectus carinatum

Summary on Marinesco-Sjogren syndrome [28]

1. Marinesco-Sjögren syndrome (MSS) is characterized by cerebellar ataxia with cerebellar atrophy, dysarthria, nystagmus, early-onset (not necessarily congenital) cataracts, myopathy, muscle weakness, and hypotonia.
2. Additional features may include psychomotor delay, hypergonadotropic hypogonadism, short stature, and various skeletal abnormalities.
3. Children with MSS usually present with muscular hypotonia in early infancy; distal and proximal muscular weakness from the first decade of life.
4. Later, cerebellar findings of truncal ataxia, dysdiadochokinesia, nystagmus, and dysarthria become apparent.
5. Motor function worsens progressively for some years, then stabilizes at an unpredictable age and degree of severity.
6. Cataracts can develop rapidly and typically require lens extraction in the first decade of life.
7. Although many adults have severe disabilities, life span in MSS appears to be near normal.

Case 8. GNE myopathy case

Description of the case 29 y, man

1. Chief complaint: distal muscle weakness
2. Past medical history: no neuromuscular disease, no consanguinity
3. Physical examination: he had predominantly distal muscle weakness and atrophy. Proximal muscle was also affected except for quadriceps muscles. Facial muscles were also spared. His hand grip strength was 10 kg(right) and 8,7 kg(left). He was not able to stand on toes or heels. He was also unable to stand up from sitting position without assistance. He could walk by himself but need rail at the stairs. DTRs were decreased.
4. Laboratory data: CK 386 IU/L (normal 62-287)
5. EMG: fibrillations, positive sharp waves, early recruitment, polyphasic units with low amplitude and short duration
6. Muscle CT: muscle atrophy in distal legs and back thighs. QF spared.

History of the illness

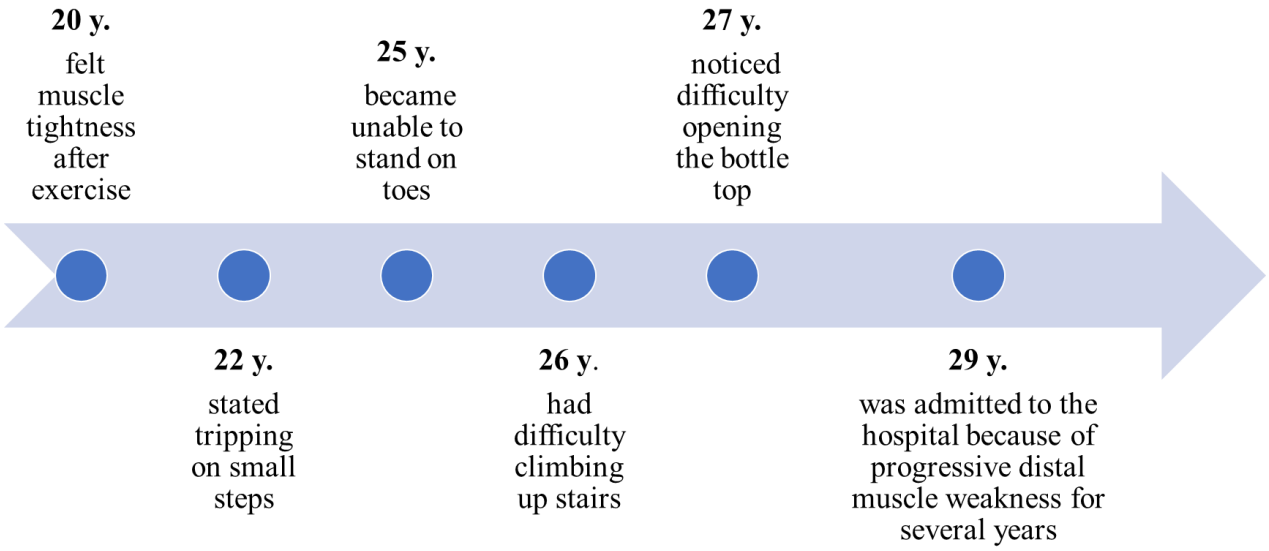
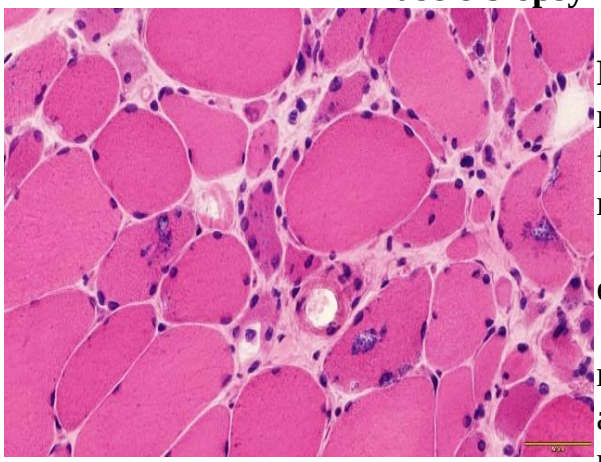


Table 8.1.

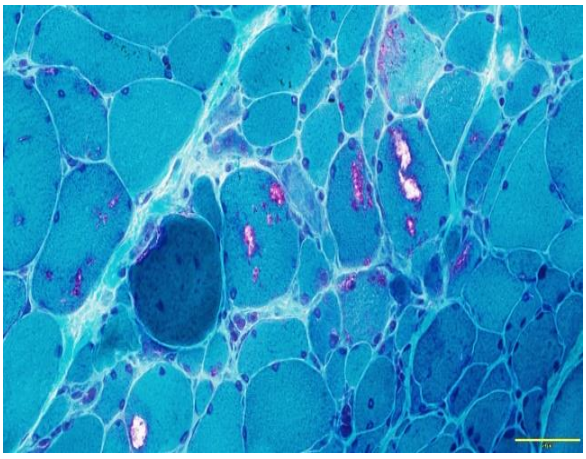
Muscle biopsy data (Pic.8)



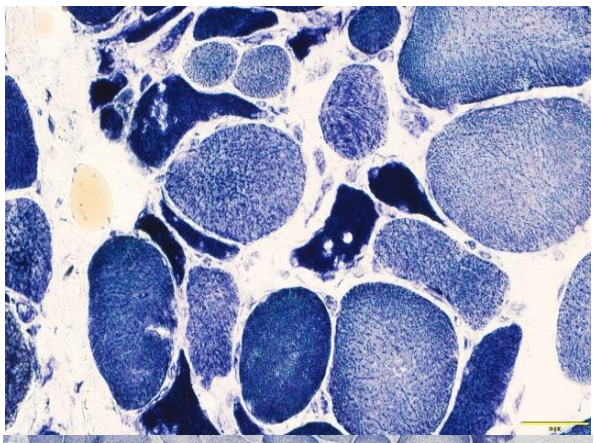
Pic.8.1. On H&E: there is a moderate to marked variation in fiber size measuring from 10 to 150 microns in diameter.

Moderate to marked endomysial fibrosis is seen.

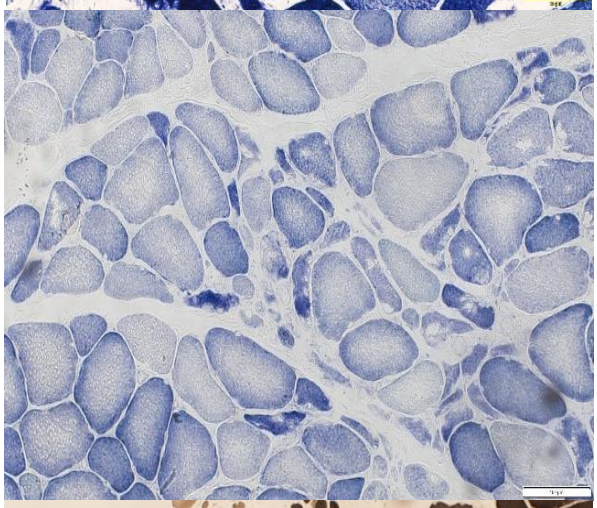
Several necrotic and some regenerating fibers are seen. There are several fibers with internalized nuclei.



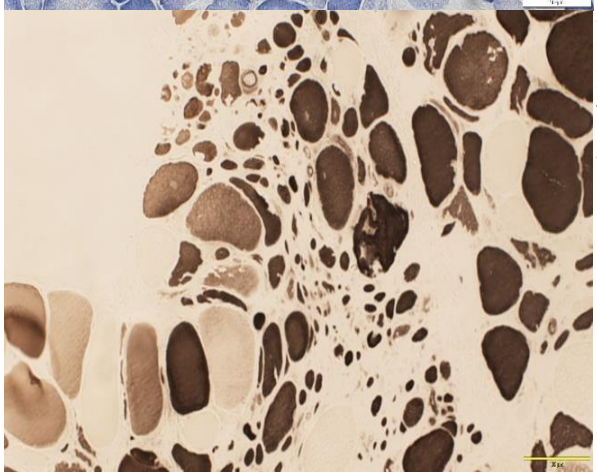
Pic.8.2. On mGT: fibers with rimmed vacuoles are scattered and a few fibers with cytoplasmic bodies are seen. RRFs are not seen. Peripheral nerve not included to this section



Pic.8.3. On NADH-TR, the intermyofibrillar networks are well organized except for atrophic muscle fibers



Pic.8.4. On SDH, strongly SDH-reactive blood vessels (SSVs) are not seen



Pic.8.5. ATPase: moderate and marked fiber type atrophy is seen in both type 1 and type 2 fibers. Some type 2 C fibers are seen

	Type 1	Type 2A	Type 2B	Type 2C
ATPase 10.4-10.7	white	brown	brown	brown
ATPase 4.6	brown	white	brown	brown
ATPase 4.2	brown	white	white	brown

Table 8.2.

Pathological diagnosis:

Myogenic change with:

1) Variation in fiber size, moderate to marked
2) Necrotic and regenerating fibers, several and some respectively
3) Fibers with internalized nuclei
4) Endomysium fibrosis, moderate to marked
5) Fibers with rimmed vacuoles, scattered
6) Fibers with cytoplasmic bodies, a few
7) Type 1 and type 2 fibers atrophy, moderate to marked
8) Type 2C fibers, some

The above findings are suggestive of myogenic condition. Together with clinical findings rise a possibility of GNE myopathy. Additional IHC and genetical analysis should be performed mutation at GNE gene found

Literature overview [29]

GNE myopathy is a progressive muscle disease caused by mutations in the GNE gene, which encodes for a key enzyme in the sialic acid biosynthesis pathway

The diagnosis should be considered primarily in patients presenting with distal weakness (foot drop) in early adulthood (other onset symptoms are possible too).

The disease slowly progresses to involve other lower and upper extremities' muscles, with marked sparing of the quadriceps.

Characteristic findings on biopsies of affected muscles include 'rimmed' (autophagic) vacuoles, aggregation of various proteins and fiber size variation.

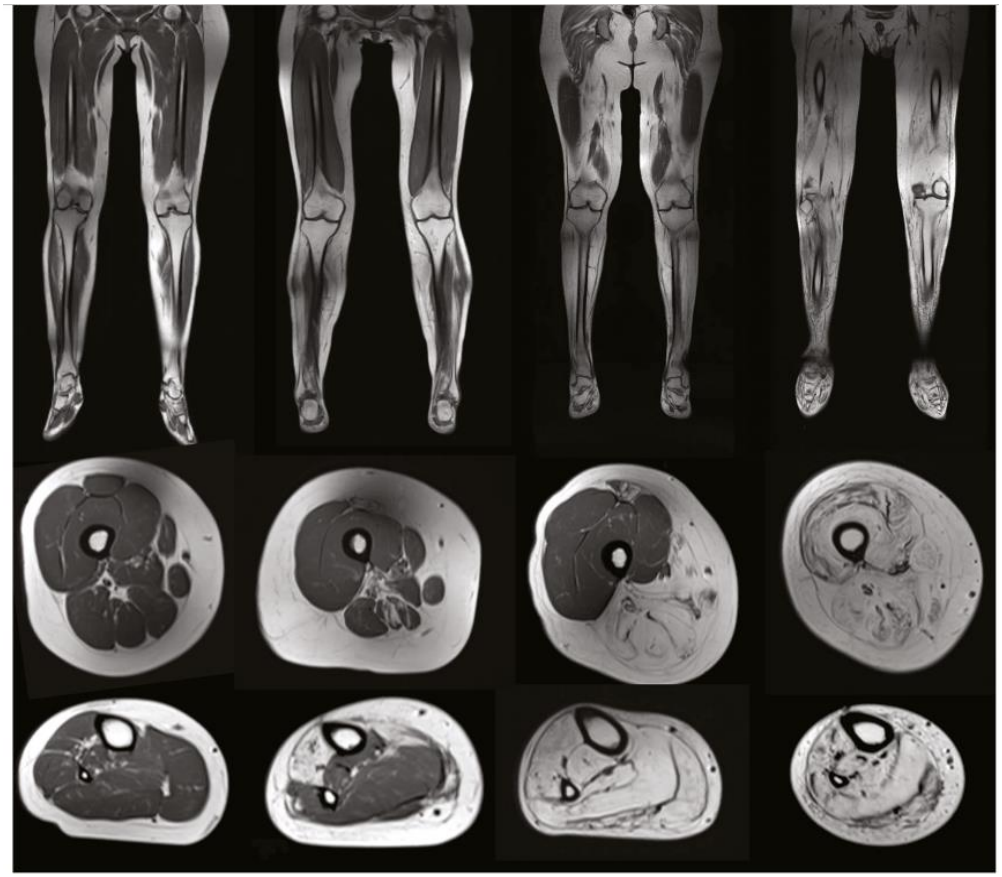
The diagnosis is confirmed by sequencing of the GNE gene

Much progress towards understanding and treating GNE myopathy has been achieved, but the final target of developing an efficacious therapy is still underway.

However, this is one of **the first human hereditary myopathies** where a logical **metabolic therapy is currently being evaluated and a gene therapy is actively developed.**

As clinical trials for potential therapies for GNE myopathy are underway, it is necessary to provide a timely diagnosis for patients with GNE myopathy.

An early diagnosis has the potential of maximizing the effect of such therapies and reducing anxiety and unnecessary testing in these patients



Pic.8.6.

Progressive muscle involvement in GNE myopathy [30].

Representative lower extremity muscle MRI images of patients with GNE myopathy, with advancing disease progression from left to right. Coronal T1-weighted muscle MRI images (upper panels). Axial T1- weighted images of the mid-femoral thigh (middle panels). Axial T1- weighted images of the lower leg (lower panels). Progressive muscle atrophy of the lower extremities is noted initially in the anterior tibialis muscle, followed by involvement of muscles in the calves and posterior thigh muscles, and finally involvement of the quadriceps in advanced stages of the disease

Conclusion

GNE myopathy, previously known as hereditary inclusion body myopathy (HIBM), or Nonaka myopathy, is a rare autosomal recessive muscle disease characterized by progressive skeletal muscle atrophy. It has an estimated prevalence of 1 to 9:1,000,000

Information resources are available at the US National Library of Medicine, including the Genetics Home Reference page (https://ghr.nlm.nih.gov/condition/inclusionbody-myopathy-2).

Finally, ClinicalTrials.gov (https:// clinicaltrials.gov) provides information on clinical studies around the world that conform with human subject and ethics review regulations.

Case 9. Inclusion body myositis case

Description of the case of 68 y, man
Chief complaint: leg muscle weakness and decreased grip power
Past medical history: benign prostate hyperplasia
Family history: no neuromuscular disease, no consanguinity
Physical examination: he had mild proximal dominant weakness. His hand grip strength was 19 kg(right) and 18 kg (left). His finger and quadriceps muscles were atrophic. Gowers' sign was present. He could walk by himself but need hand rail at the stairs. DTRs were decreased. He had no neck weakness. He had no involvement in facial muscles. His speech was normal. He had difficulty swallowing solids.
Laboratory data: CK: 378 IU/L (normal 62-287)
EMG: myopathic changes in biceps brachii and rectus femoris

Muscle CT: muscle atrophy at forearm and thigh muscles

History of the illness

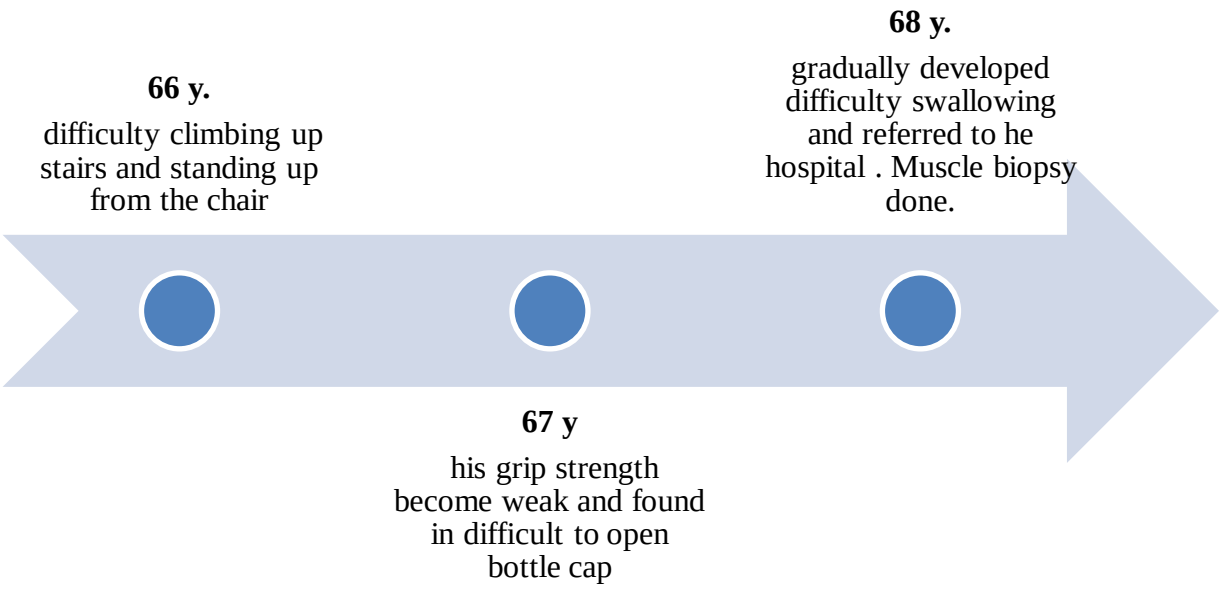
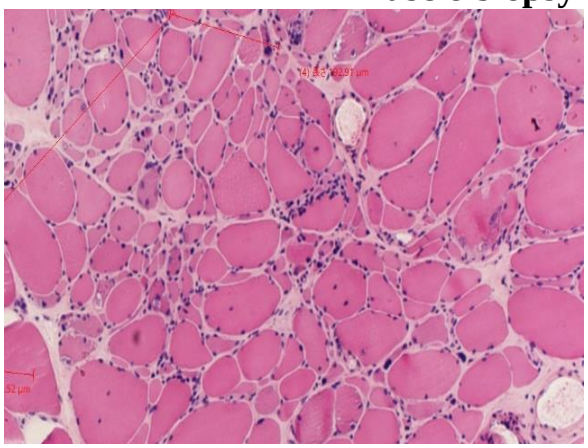
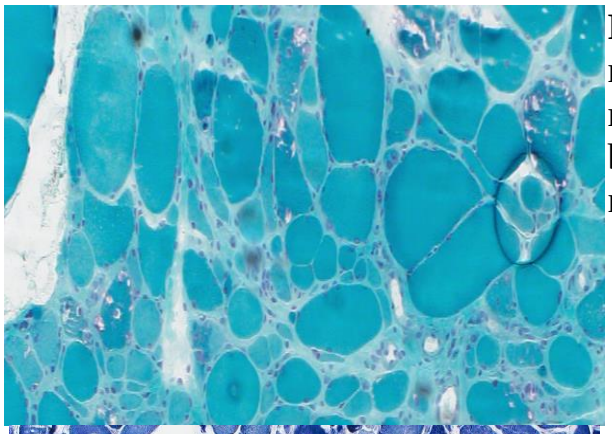


Table 9.1.

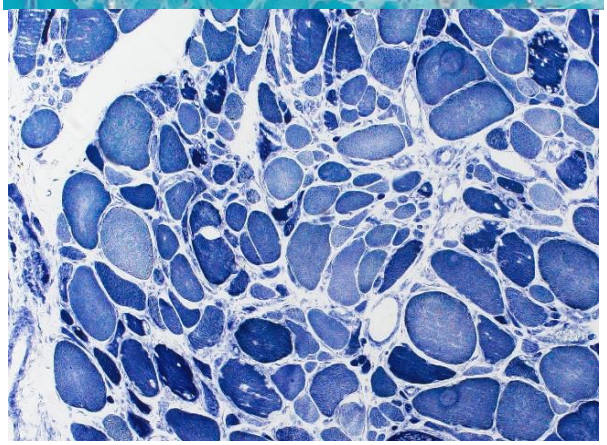
Muscle biopsy data (Pic.9)



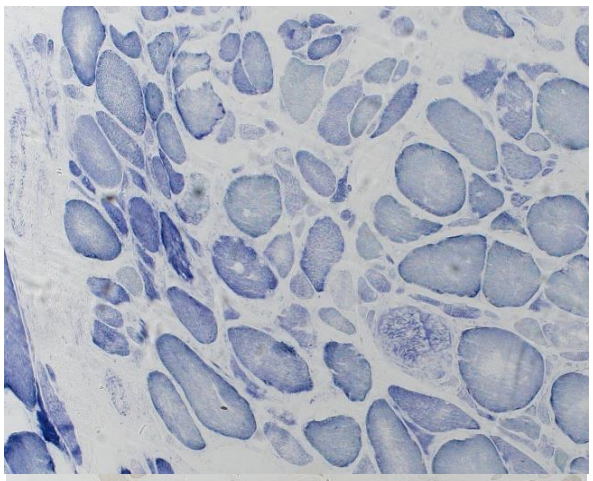
Pic.9.1. On H&E: fiber size variation is moderate to marked, measuring from 7 to 96 microns in diameter. A few necrotic and some regenerating fibers are seen. Mild mononuclear cellular infiltration is seen. Marked endomysial fibrosis is seen. There are some fibers with internalized nuclei



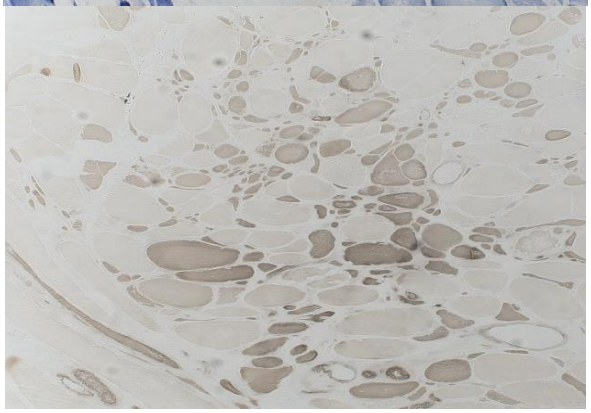
Pic.9.2. On mGT: some fibers with rimmed vacuoles are seen, ragged red fibers (RRGs), nemaline bodies are not seen. Peripheral nerve not included to the section**.**



Pic.9.3. On NADH-TR, the intermyofibrillar networks are mildly disorganized

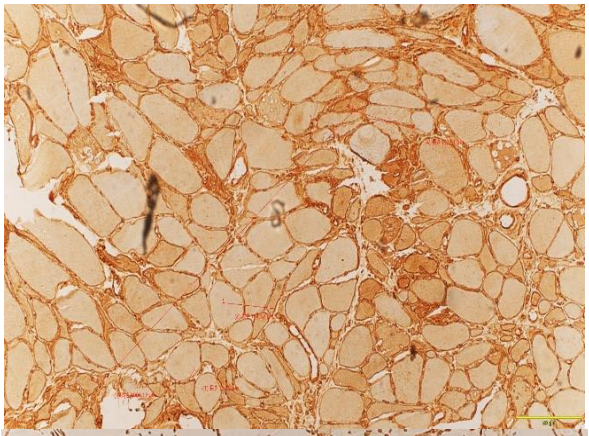


Pic.9.4. On SDH, strongly SDH-reactive blood vessels (SSVs) are not seen

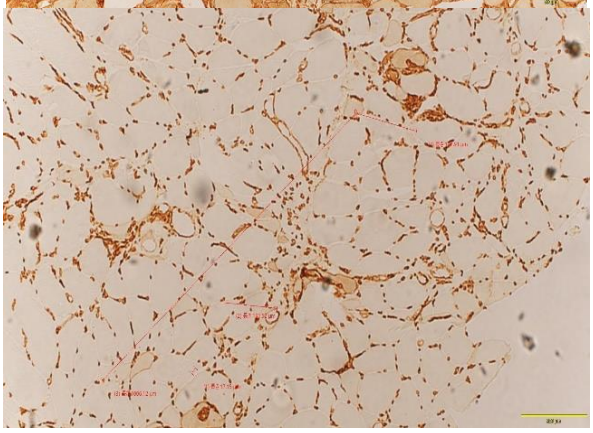


Pic.9.5. On ATPase, Marked type 2 fibers atrophy. Type 2C are scattered

Immunohistochemistry



Pic.9.6. HLA-ABC markedly elevated



Pic.9.7. HLA-DR markedly elevated

Pathological diagnosis

Myopathic change with:

1. Fiber size variation, moderate to marked
2. Necrotic fibers, a few
3. Regenerating fibers, some
4. Endomysial fibrosis, marked
5. Fibers with internalized nuclei, some
6. Fibers with rimmed vacuoles, some
7. Type 2 fiber atrophy, marked
8. Type 2C fibers, scattered

Comments: the above findings reflect to chronic myopathic process.

Key findings
Age of onset (66y)
Quadriceps and finger flexors weakness
Difficulties of swallowing of solids
CT muscle atrophy at forearm and thigh muscles
Pathomorphological chronic myopathic process
Fibers with rimmed vacuoles
On IHC fibers with HLA-ABC and DR expression
All above findings are key features of IBM

Main considerations on IBM [30,31,32]

IBM progresses slowly and is commonly misdiagnosed initially as arthritis or polymyositis; IBM is associated with cardiovascular complications and other autoimmune diseases and has a high economic cost.

IBM characteristic early involvement of quadriceps and long finger flexors. Less common presentations (eg, dysphagia), however, are important to recognize.

IBM has finger flexor and knee extensor weakness and invasion of myofibers by cytotoxic T cells that distinguish it from most other muscle diseases.

Clinical assessment complemented by muscle's MRI is useful in choosing the optimal muscle to biopsy.

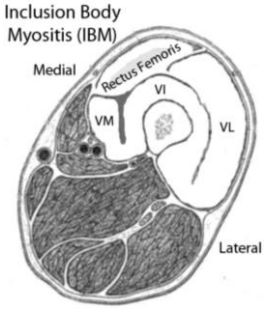
IBM has a greater range of autoimmune T cell abnormalities than any other muscle disease;

Clinicopathologic correlation is imperative in interpretation of the muscle biopsy and guiding further staining.

MRI also can be useful in delineating patterns of muscle involvement to differentiate IBM from other primary muscle conditions, like inherited myopathies.

Inflammatory features on muscle biopsy can be seen in the idiopathic inflammatory myopathies (polymyositis, dermatomyositis, IBM, and immune-mediated necrotizing myopathies) and in some inherited muscle conditions, such as facioscapulohumeral muscular dystrophy, and other genetic muscular dystrophies, in particular dysferlinopathies

Neuroimaging findings[32]



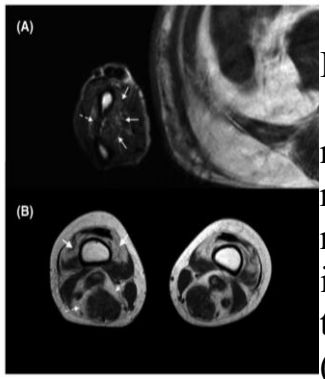
General features: Asymmetry

Arms: Flexor digitorum profundus

Thigh: Sartorius, Quadriceps

Leg: Gastrocnemius, medial

https://neuromuscular.wustl.edu/



Axial plane, T1 IBM patient

(A) Upper limbs muscle with a mild fatty replacement of the muscles of the forearm, involving predominantly the deep flexor digitorum (full arrows), and to a lesser extent the extensors (dashed arrows).

(B) Lower limbs muscle with a distal involvement muscle atrophy (loss of volume with the widening of the fat tissue between muscles, dashed arrows) and fatty replacement occurring mainly in the quadriceps femori muscle (full arrows).

Table 9.2.

Conclusion

Degenerative abnormalities that can occur in IBM include numerous myofiber protein aggregates associated with endoplasmic reticulum stress.

Treatment refractoriness probably reflects the inability of current therapies to inhibit or deplete the highly differentiated population of effector memory and terminally differentiated effector T cells present in IBM

Mounting evidence that IBM is an autoimmune T cell-mediated disease provides hope that future therapies directed towards depleting these cells could be effective.

Case 10. Immune-mediated necrotizing myopathy case

Description of case of 35 y woman

Chief complaint: Leg muscle weakness and decreased grip power

Family history: no neuromuscular disease, no consanguinity

Physical examination: she had prominent proximal dominant weakness of 2-3 on MRS scale. Distal muscle strength was reported to be normal. No calf hypertrophy or atrophy was seen. Gowers' sign was positive. She showed waddling gait. DTRs were decreased. Facial muscles were not involved. Dysphagia or dysarthria was not seen.

Laboratory data: CK 7930 IU/L(normal 45-163), **Antibodies**: Jo-1(-), ANA (-)

EMG: Early recruitment, fibrillation and positive sharp waves, low polyphasic units. CRD in some muscles.

History of the illness

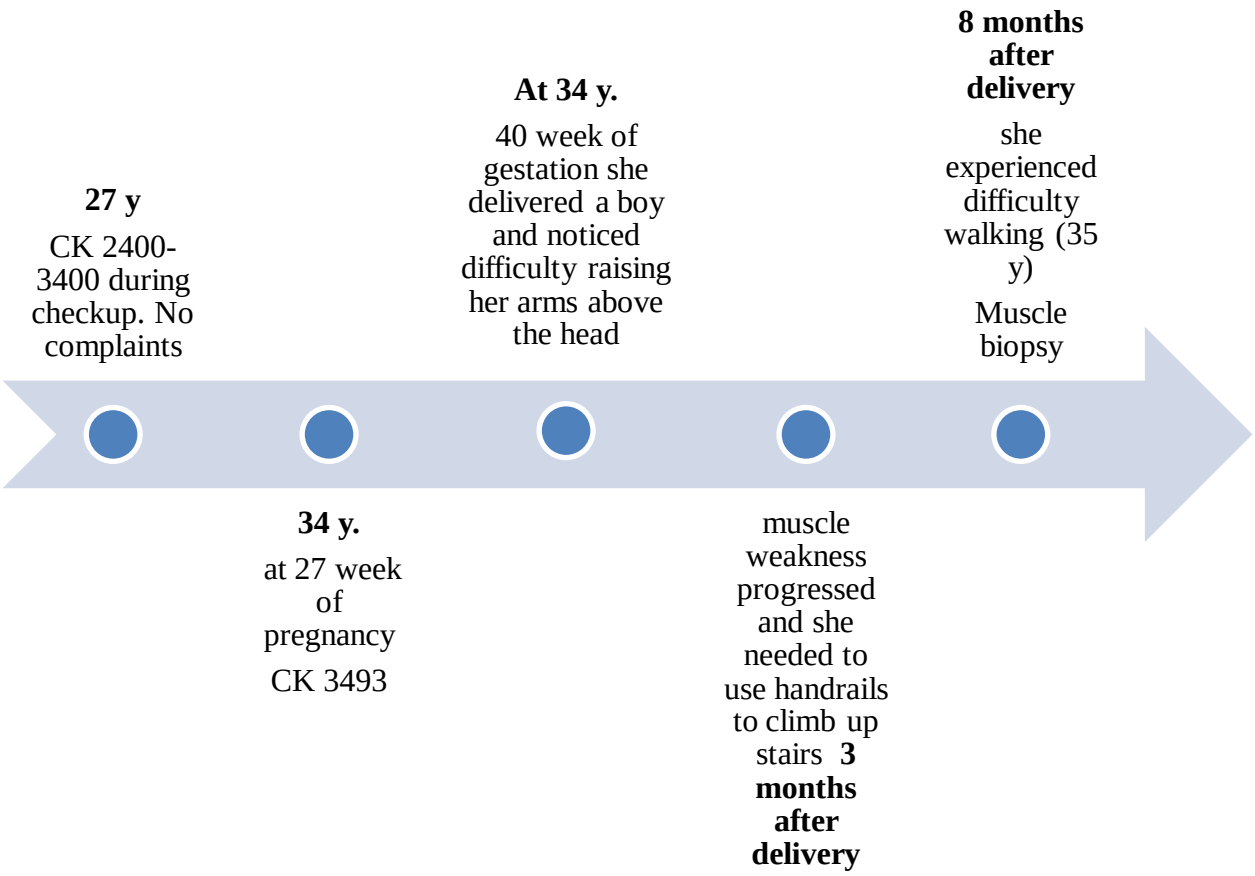
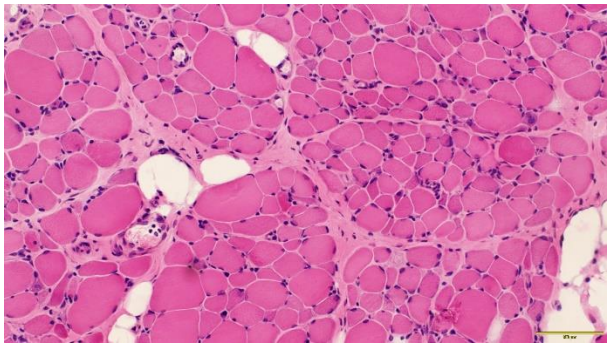
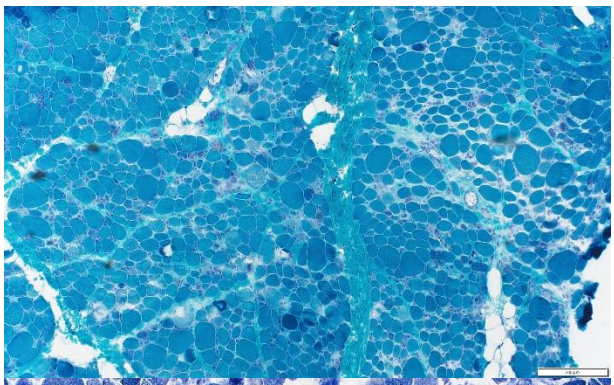


Table 10.1.

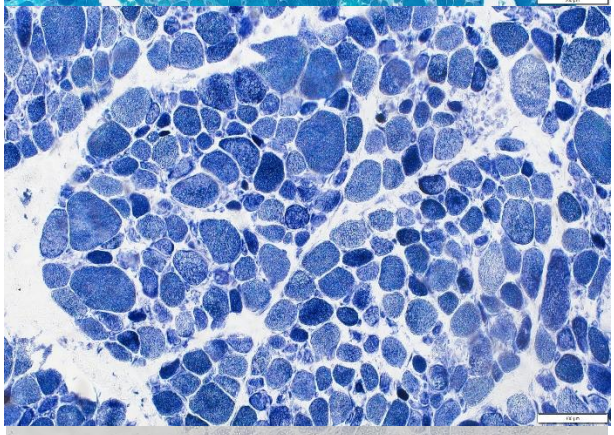
Muscle biopsy data (pic.10)



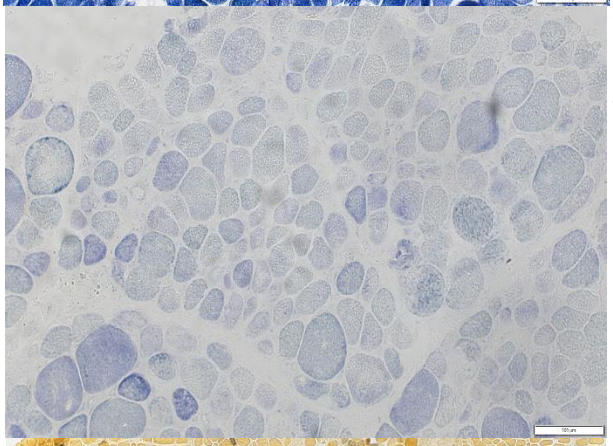
Pic.10.1. On H&E, there is a moderate to marked variation in fiber size measuring from 8 to 80 microns in diameter. Some necrotic and regenerating fibers are seen. Some fibers with internalized nuclei are seen. Mild reactive lymphocyte infiltration is seen. Marked endomysial fibrosis is seen.



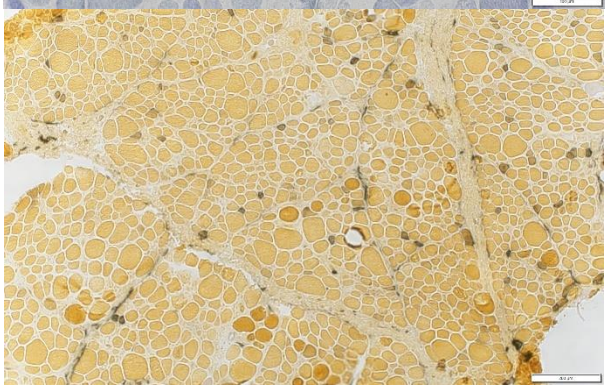
Pic.10.2. On mGT, nemaline bodies, ragged-red fibers and rimmed vacuoles are not seen. Peripheral nerve is not included to this section.



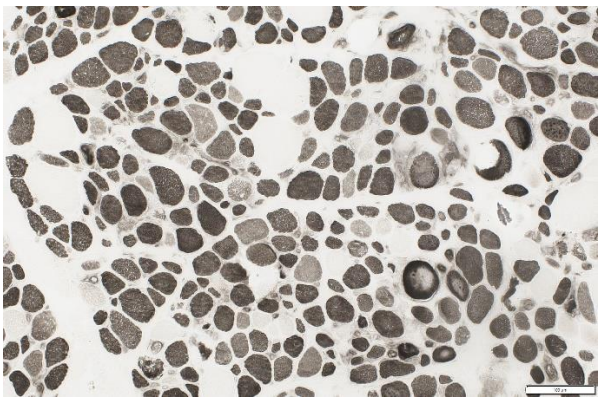
Pic.10.3. On NADH, intermyofibrillar networks are disorganized especially in atrophic fibers



Pic.10.4. On SDH, no strongly SDH-reactive vessels (SSVs) are highlighted.



Pic.10.5. On ALP, enzymatic activity is mildly seen in perimysium and regenerating fibers (arrow)



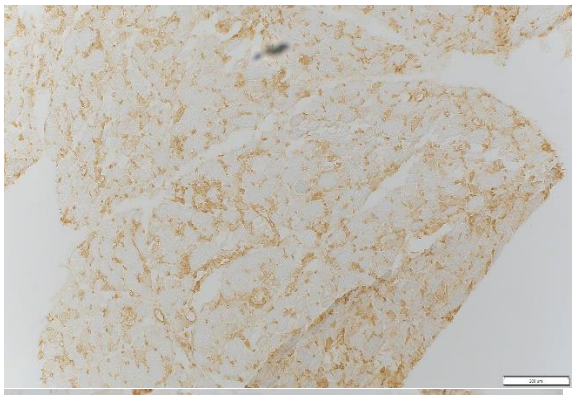
Pic.10.6. On ATPase, marked type 2 fibers atrophy is seen, type 2 C fibers are scattered

Myopathic changes with:

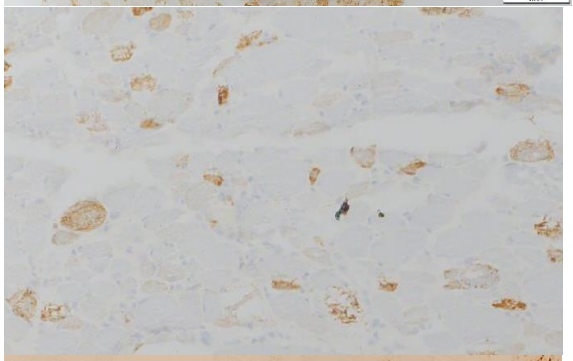
1. Fibers size variation, moderate to marked.
2. Necrotic and regenerating fibers, some
3. Fibers with internalized nuclei, some
4. Endomysial fibrosis, marked
5. Type 2 fibers atrophy, marked
6. type 2 C fibers, scattered

Conclusion: The above findings reflect chronic necrotic and regenerating processes.

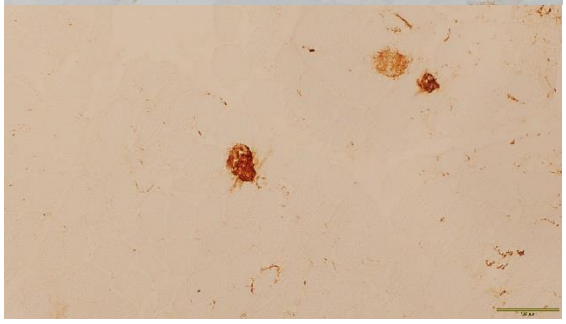
Immunohicstochemistry



Pic.10.7. HLA-ABC is positive



Pic.10.8. p62 diffuse granular deposition



Pic.10.9. MAC: scattered fibers with deposition on sarcolemma

On IHC there are scattered fibers with MAC deposition on sarcolemma, on p62 diffuse granular deposition these are suggestive o**f immune mediated necrotizing myopathy.**

Key findings from this case

1. Unexplained elevation of CK 2400-3400 IU/L at 27 years
2. Pregnancy and delivery as a trigger at 34 years
3. Chief compliance: progressive muscle weakness
4. Elevation of CK up to 7930 IU/L
5. EMG: Early recruitment, fibrillation and positive sharp waves, low polyphasic units. CRD in some muscles.
6. Muscle biopsy findings reflect to chronic necrotic and regenerating processes
7. On IHC there are scattered fibers with MAC deposition on sarcolemma, on p62 diffuse granular deposition.

All above suggestive of immune mediated necrotizing myopathy

Diagnostical algorithm

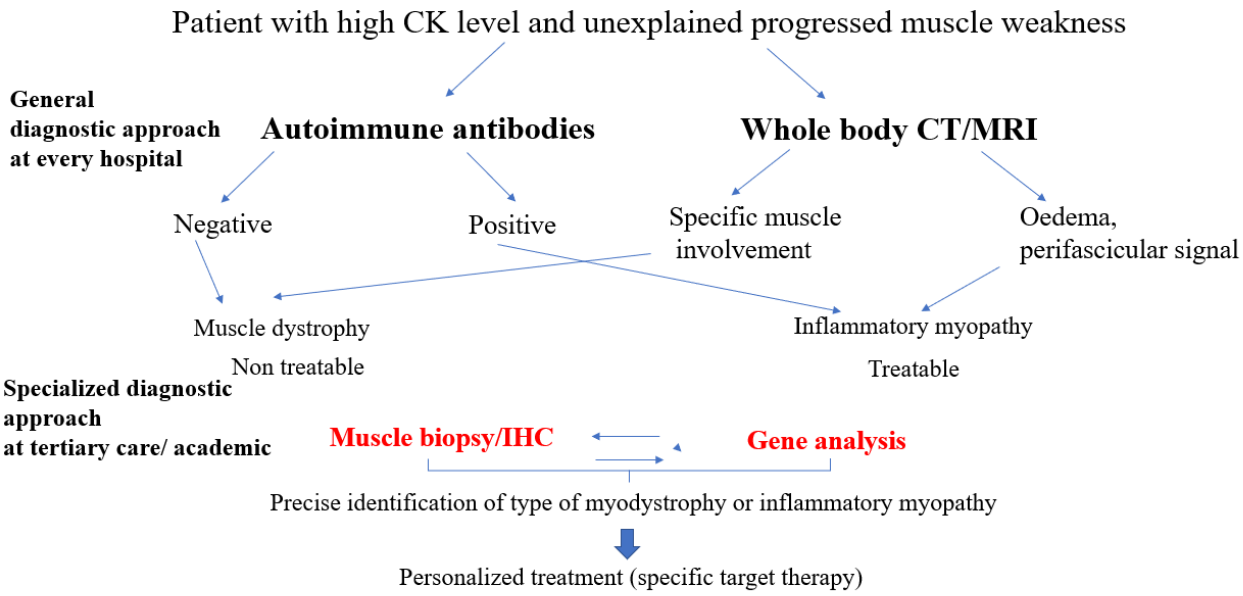


Table 10.2.

Summary[21]

Immune- mediated necrotizing myopathy (IMNM) has emerged as a novel entity among the inflammatory myopathies.

This is a group of myopathies are associated with anti-signal recognition particles(anti-SRP) autoantibodies and in some cases with malignancy, statin treatment or active viral infection.

Children, adolescence and adults are suffering

Clinical: proximal muscle weakness, usually acute or subacute onset, slowly progressive course mimicking limb-girdle muscular dystrophy, CK level >3000 IU/L

Muscle biopsy with IHC could help in diagnosis

Poor response to steroids but other immunosuppressive drugs may be efficient.

Case 11. Mitochondrial disease case

Description of the case of 12 y 4 m, female

Chief complaint: ptosis, ophthalmoplegia

Past medical history: Negative

Family history: No neuromuscular disease

Physical examination: height is 114 sm and weight is 18,9 kg. IQ on borderline level. Sensoneural hearing loss. Hirsutism is noted in the lower back. Ptosis and nearly complete ophthalmoplegia. No limb muscle weakness. Unable to perform tandem gait.

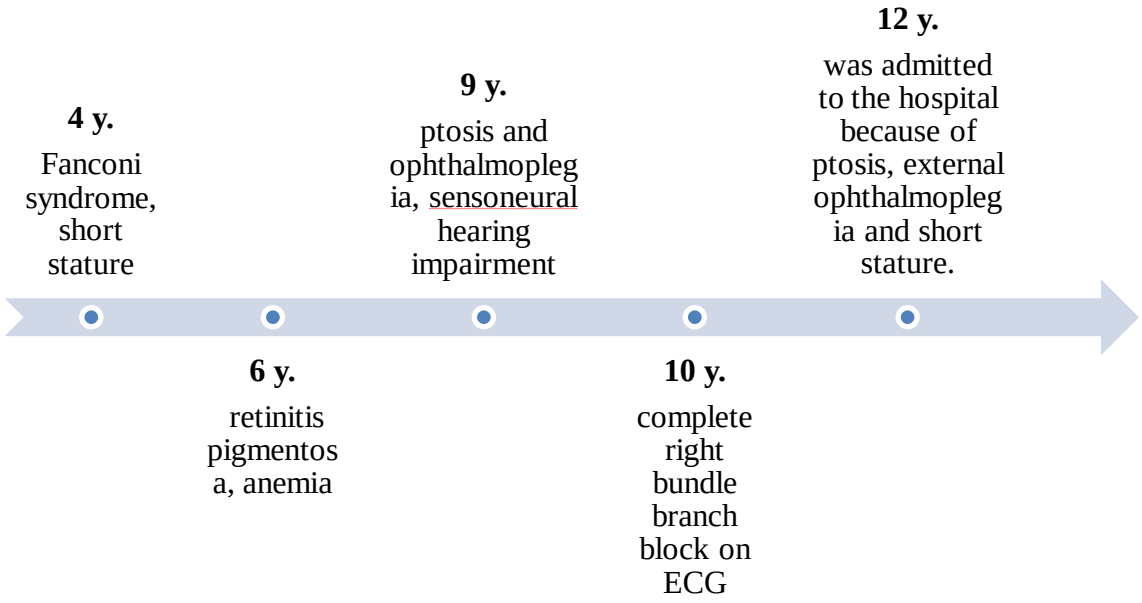
Laboratory data: CK: 66 IU/L (normal: 45-163) Lactate(blood) 27,7; (CSF) 44,8 (3.0-17.0)

Optic fund: retinitis pigmentosa

ABR: wave 2 absent

ECG: CRBBB

History of the illness



What we have after analysis of clinical data:

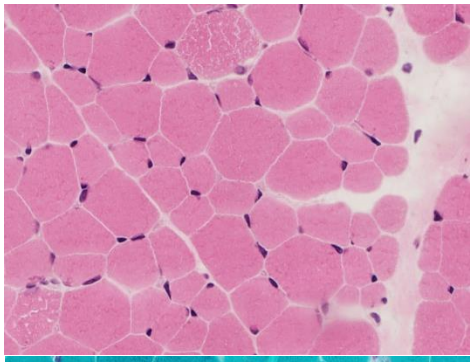
Ptosis, ophthalmoplegia, short stature (height 114 sm and weight 18,9 kg <3 δ), IQ on borderline level. Sensoneural hearing loss (auditory brainstem response: wave 2 absent), Hirsutism in the lower back. No limb muscle weakness. Unable to perform tandem gait, retinitis pigmentosa, lactate acidosis(Lactate(blood) 27,7 ↑; (CSF) 44,8 ↑(3.0-17.0), arrythmia(CRBBB(complete right bundle branch block)

Normal child at early childhood. Disease onset at 4 y. gradually progression of the symptoms, multisystem involving

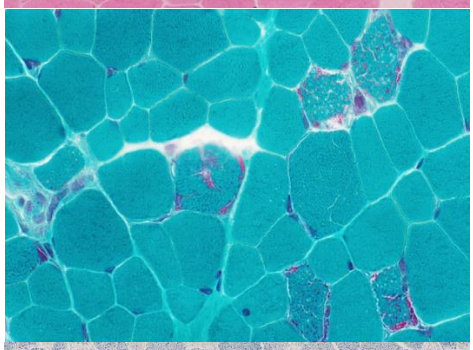
Suspicion on mitochondrial disorder

How to prove?

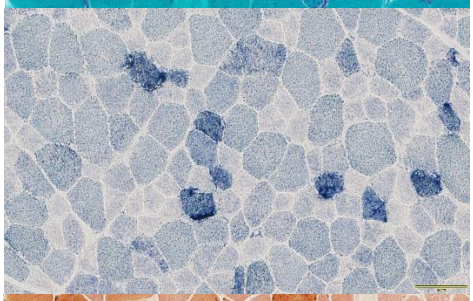
Muscle biopsy data (Pic.11)



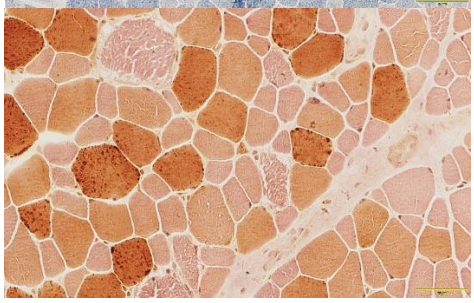
Pic.11.1. On H&E: There is a mild variation in fiber size measuring from 20 to 70 microns in diameter. No endomysial fibrosis is seen. Some fibers have granular structure.



Pic.11.2. On mGT: there are some ragged-red fibers (RRFs). Rimmed vacuoles or nemaline bodies are not seen. Peripheral nerve bundles are well-myelinated



Pic.11.3. On SDH: RRFs are seen, strongly SDH-reactive blood vessels (SSVs)are not seen



Pic.11.4. On cytochrome C oxidase, there are focal COX- negative RRFs

Pathological findings:

1. Myopathic change with:
2. 1) variation in fiber size, mild
3. 2)RRFs focal COX-negative, some
4. 3) type 2c fibers, some

Comment: the above findings are suggestive to mitochondrial pathology. Gene analysis is recommended Chronic progressive external ophthalmoplegia(CPEO)!

An overview of literature information[33]

CPEO is a slowly progressing mitochondrial disease.

It may begin at any age and progresses over a period of 5–15 years.

The first presenting symptom of ptosis is often unnoticed by the patient until the lids droop to the point of producing a visual field defect.

Often, patients will tilt the head backwards to adjust for the slowly progressing ptosis of the lids.

In addition, as the ptosis becomes complete, the patients will use the frontalis (forehead) muscle to help elevate the lids.

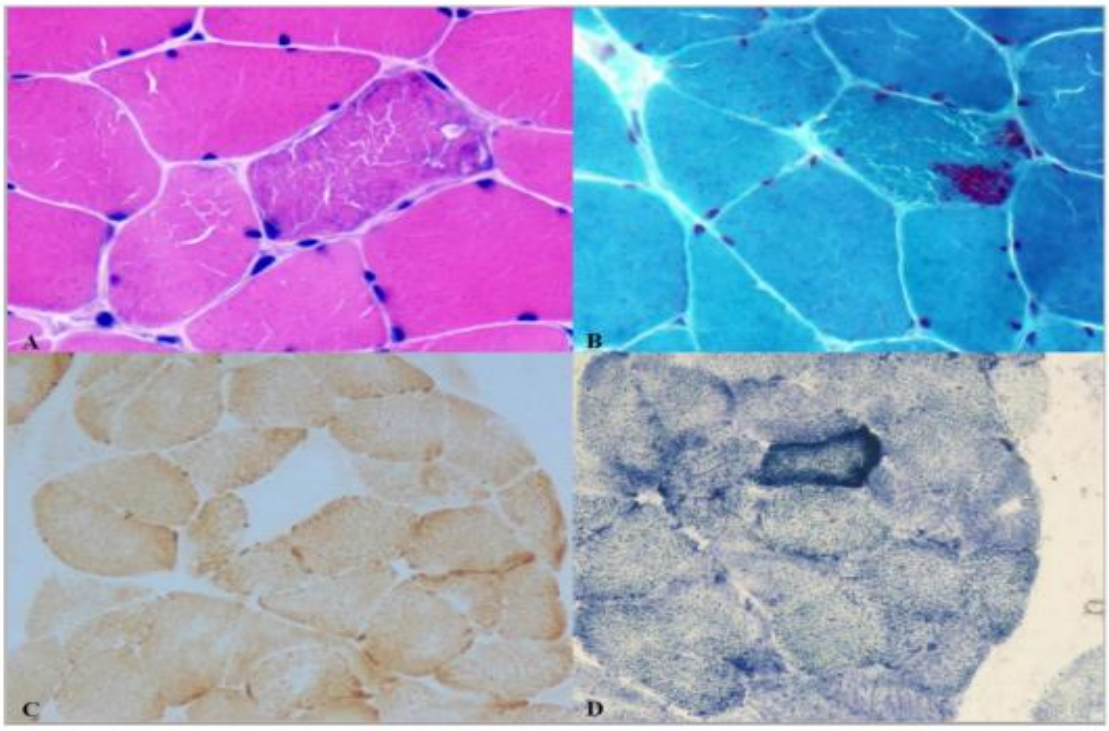
CK levels can range from normal to mildly or moderately increased

Typical mitochondrial syndromes [34]

Syndrome	Relative Frequency	Typical Feature(s)	Associated Feature(s)	Inheritance	Most Frequent Genetic Findings	Treatment of Choice
Alpers syndrome	Very rare	Childhood myocerebrohepatopathy		Autosomal recessive	*POLG* mutations with secondary mtDNA depletion	Symptomatic (avoid valproate)
Autosomal dominant optic atrophy (ADOA)	Rare	Optic neuropathy (blindness)		Autosomal dominant	*OPA1* mutations	Symptomatic
Coenzyme Q10 deficiency	Very rare	Ataxia or myopathy or multi-system disease		Autosomal recessive	Various nuclear genes	Coenzyme Q10
Kearns–Sayre Syndrome (KSS)	Frequent	Ocular myopathy (ptosis, ophthalmoparesis)	Ataxia, cardiac conduction defects	Sporadic	Single large-scale deletion of mtDNA	Symptomatic
Leber hereditary optic neuropathy (LHON)	Very frequent	Optic neuropathy (blindness)		Maternal (low penetrance, higher in male smokers)	Various mtDNA mutations	Idebenone
Leigh syndrome	Frequent	Severe pediatric encephalopathy		Autosomal recessive, X-linked or maternal	Various nuclear or mtDNA mutations (e.g., m.8993T > G)	Symptomatic
Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS)	Frequent	Stroke-like episodes	Cardiac involvement, hearing loss, diabetes	Maternal	m.3243A > G	Symptomatic
Myoclonic encephalopathy with ragged-red fiber (MERRF)	Frequent	Myoclonus	Ataxia, myopathy	Maternal	m.8344A > G	Symptomatic (e.g., Levetiracetam)
Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE)	Very rare	Gastrointestinal dysmotility	Leukodystrophy, ocular myopathy, peripheral neuropathy	Autosomal recessive	*TYMP* mutations	Liver transplantation

Table 11.1.

Histological findings in mitochondrial myopathy[35]



Pic.11.5.

(A,B) Ragged red fiber (Hematoxylin– Eosin and Gomori's staining, respectively, at the center of each panel), (C) cytochrome c oxidase (COX)-negative fibers ("white" fibers, COX staining), and (D) "Ragged blue" fibers (SDH (succinate dehydrogenase) staining)

RRFs

	mGT	SDH	COX
	RRFs	Strongly SDH reactive Blood vessels (**SSV**)	Focal **COX deficiency**
CPEO	+	-	COX-negative RRFs (all RRFs: COX-negative)
MERRF	+	+	COX-negative RRFs (all RRFs: COX-negative) COX-negative SSVs (all SSV: COX-negative)
MELAS	++	+	COX-variable RRFs COX-variable SSVs
Leigh	-	-	- (90%) ※10% (*SURF1*, etc.): COX complete deficiency

subtype	mtDNA/gDNA	Onset-age Average [Range]	Elevated CSF lactate
CPEO (chronic progressive external ophthalmoplegia)	**Single large deletion** (de novo) <70%> **Point mutation** (maternal): ex. m.3243A>G (COX-variable RRFs but no SSV) **Multiple deletion** (due to **gDNA gene**) **gDNA gene** (*ANT1*, *POLG*, *TP*, etc.)	>20y *KSS: <20y	Mild
MERRF (Myoclonus epilepsy associated with ragged-red fibers)	**Point mutation** (maternal): **m.8344A>G** (frequent), m.3243A>G, etc.	24y [6 to 48]	Mild to moderate
MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes)	**Point mutation** (maternal): **m.3243A>G** <80%>, m.3271A>G, m.13513G>A, et	10y [2 to 40]	Mild to moderate
Leigh syndrome	**Point mutation** (maternal): <20%> m.8993T>G or C (Ho), m.9176T>G or C (Ho) <15%>, m.13513G>A (He), m.3243A>G (He), m.8344A>G (He) **gDNA gene** (*SURF1* <10%>, *PDHA1* <10%>, etc.)	Infantile to childhood	Marked (L/P >20, Normal L/P: PDHC)

*KSS (Kearns-Sayre Syndrome): external ophthalmoplegia, retinitis pigmentosa, conduction defects of the heart
Ho: homoplasmy, He: heteroplasmy

Table 11.2.

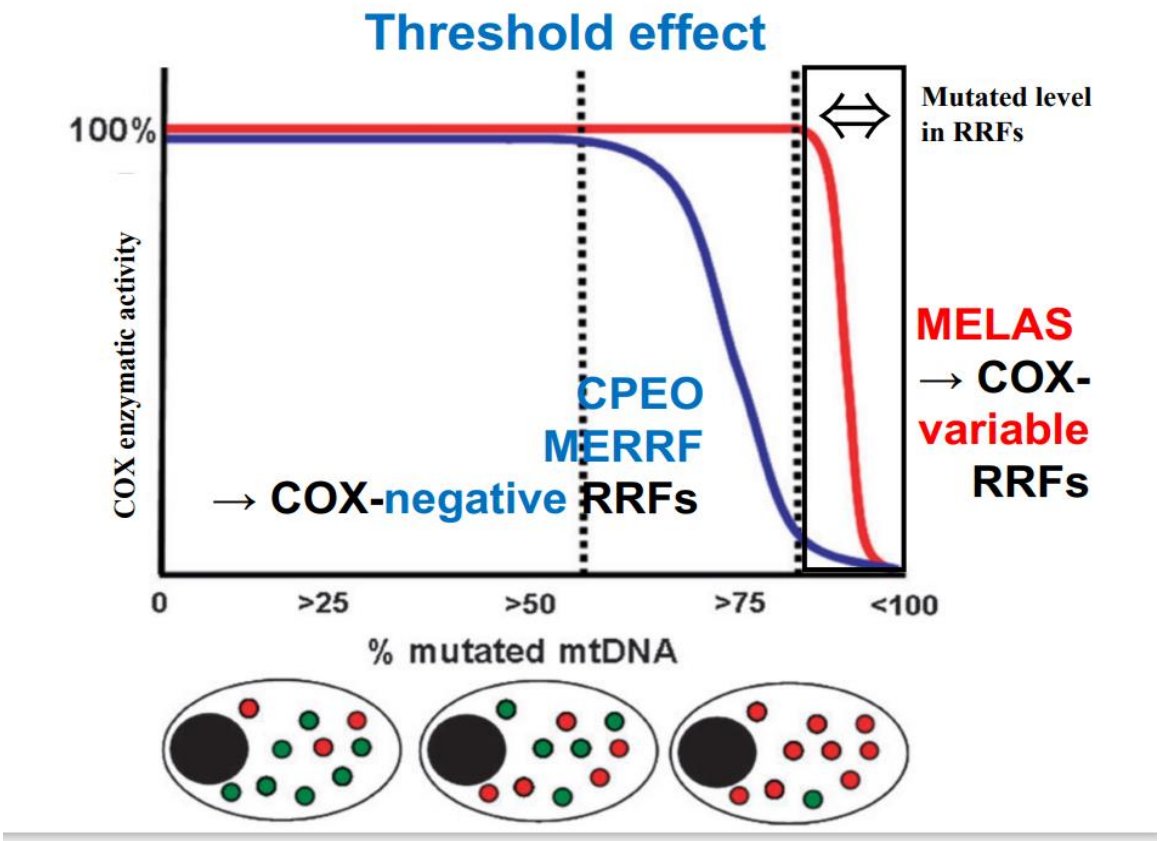


Table 11.3.

Mitochondrial manifestations[36,37]

The prevalence of mitochondrial diseases is at least 1:8500 of all live births.

The clinical features of MD are not specific and are variable between patients, including neurological and non-neurological presentations.

MELAS, a common MD, is a progressive syndrome where patients can recover **from one phenotype and develop others later.**

Subjects with mtDNA mutations can be asymptomatic or have multi-organ involvement

Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a major clinical entity encompassing mitochondrial diseases resulting from mitochondrial dysfunction.

The prevalence of MELAS syndrome has been estimated to be 0.18:100,000 in Japan, 1.41:100,000 in the north east of England, 2:100,000 in Sweden, 18.4:100,000 in Finland, and 236:100,000 in Australia.

The onset ages of MELAS syndrome:

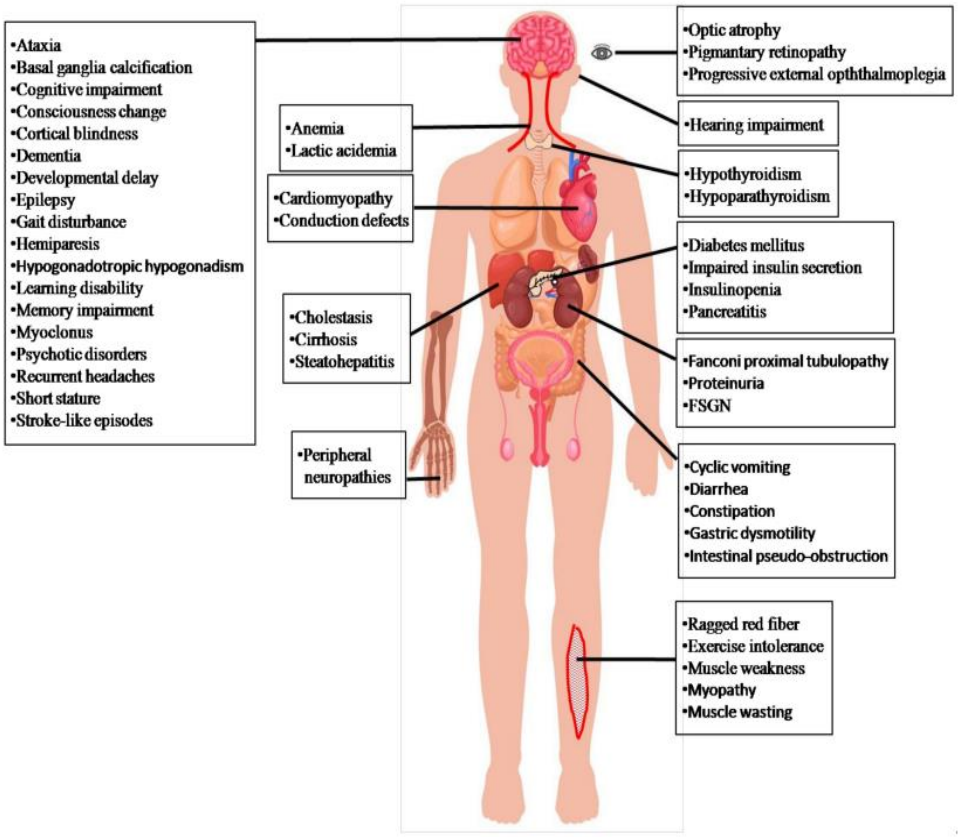
- **65–76% before 20 years,**
- 5–8% before 2 years,
-1–6% after 40 years,

Clinical presentations of MELAS syndrome are **more common in children** than in adults [35]

Stroke-like episodes, the most critical symptom of MELAS, are characterized by an abrupt onset of cortical neurological deficits with typical MRI abnormalities not conforming to the distribution of main arteries

A possible pathogenesis of stroke -like episodes shown below [38]

Pic.11.6.


•Ataxia
•Basal ganglia calcification
•Cognitive impairment
•Consciousness change
•Cortical blindness
•Dementia
•Developmental delay
•Epilepsy
•Gait disturbance
•Hemiparesis
•Hypogonadotropic hypogonadism
•Learning disability
•Memory impairment
•Myoclonus
•Psychotic disorders
•Recurrent headaches
•Short stature
•Stroke-like episodes
•Anemia
•Lactic acidemia
•Cardiomyopathy
•Conduction defects
•Cholestasis
•Cirrhosis
•Steatohepatitis
•Peripheral neuropathies
•Optic atrophy
•Pigmantary retinopathy
•Progressive external opththalmoplegia
•Hearing impairment
•Hypothyroidism
•Hypoparathyroidism
•Diabetes mellitus
•Impaired insulin secretion
•Insulinopenia
•Pancreatitis
•Fanconi proximal tubulopathy
•Proteinuria
•FSGN
•Cyclic vomiting
•Diarrhea
•Constipation
•Gastric dysmotility
•Intestinal pseudo-obstruction
•Ragged red fiber
•Exercise intolerance
•Muscle weakness
•Myopathy
•Muscle wasting

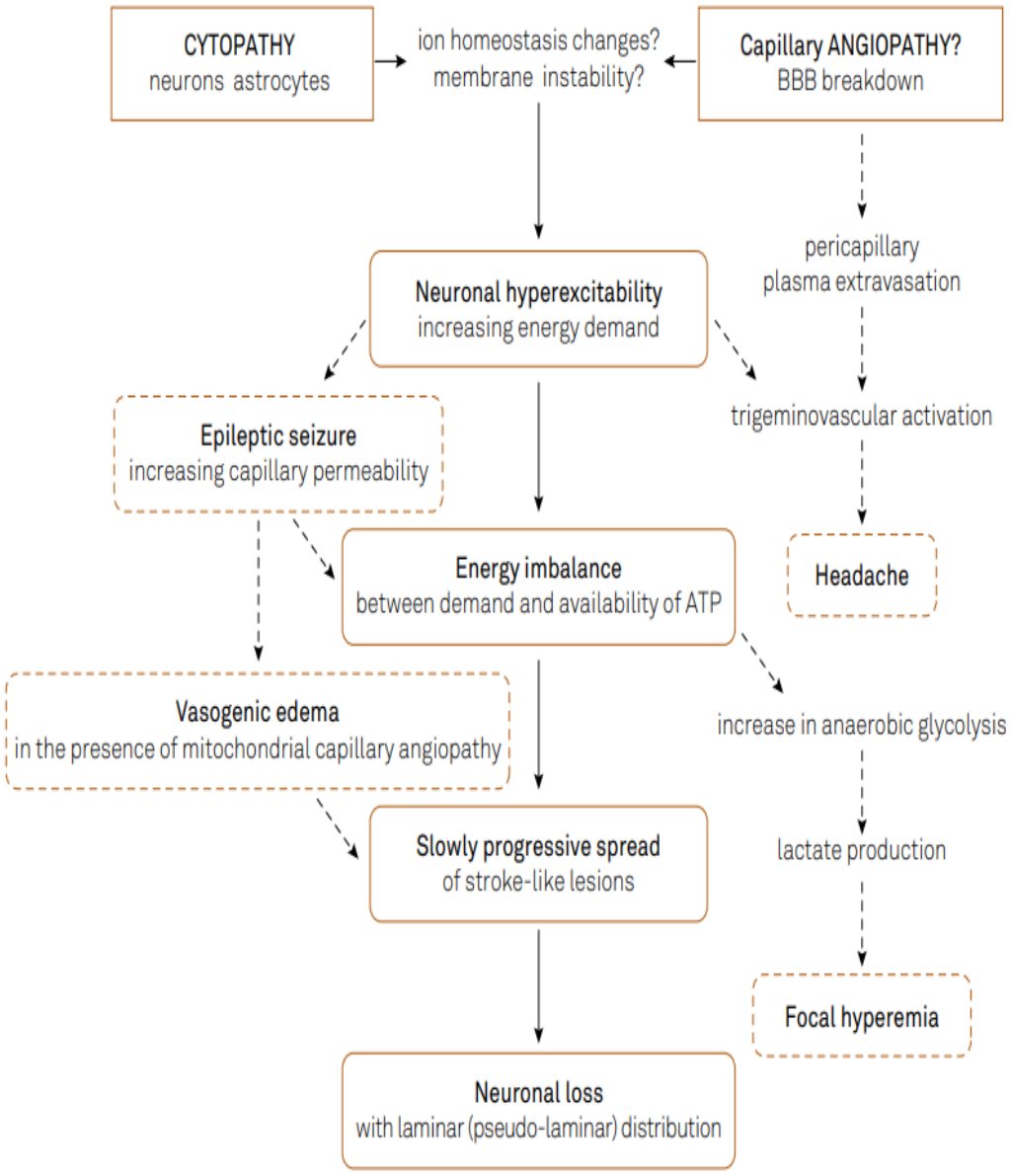
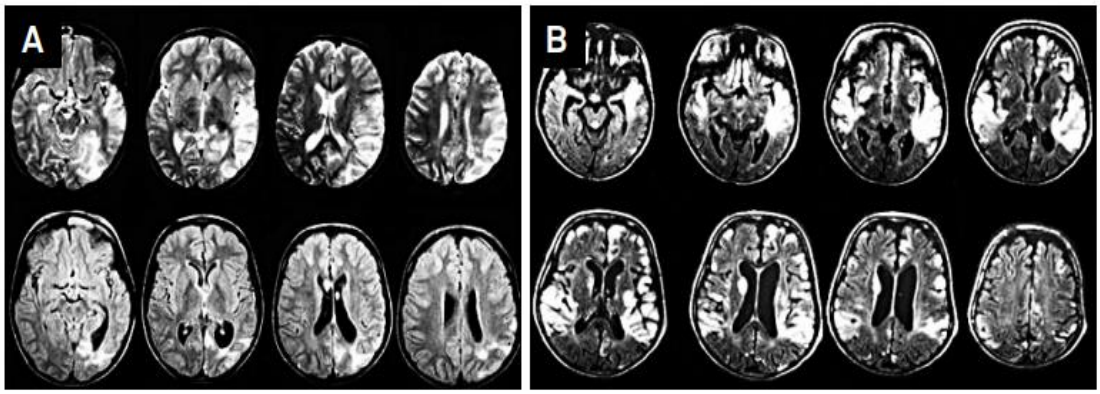


Table 11.4.

Imaging data of MELAS



Pic.11.7.

Imaging features in brain MRI showing unilateral (A) or bilateral (B) lesions in MELAS patients from Arq Neuropsiquiatr 2009; 67:668-676

Management of MELAS[36]

Multidisciplinary approach including social workers and physical therapists.

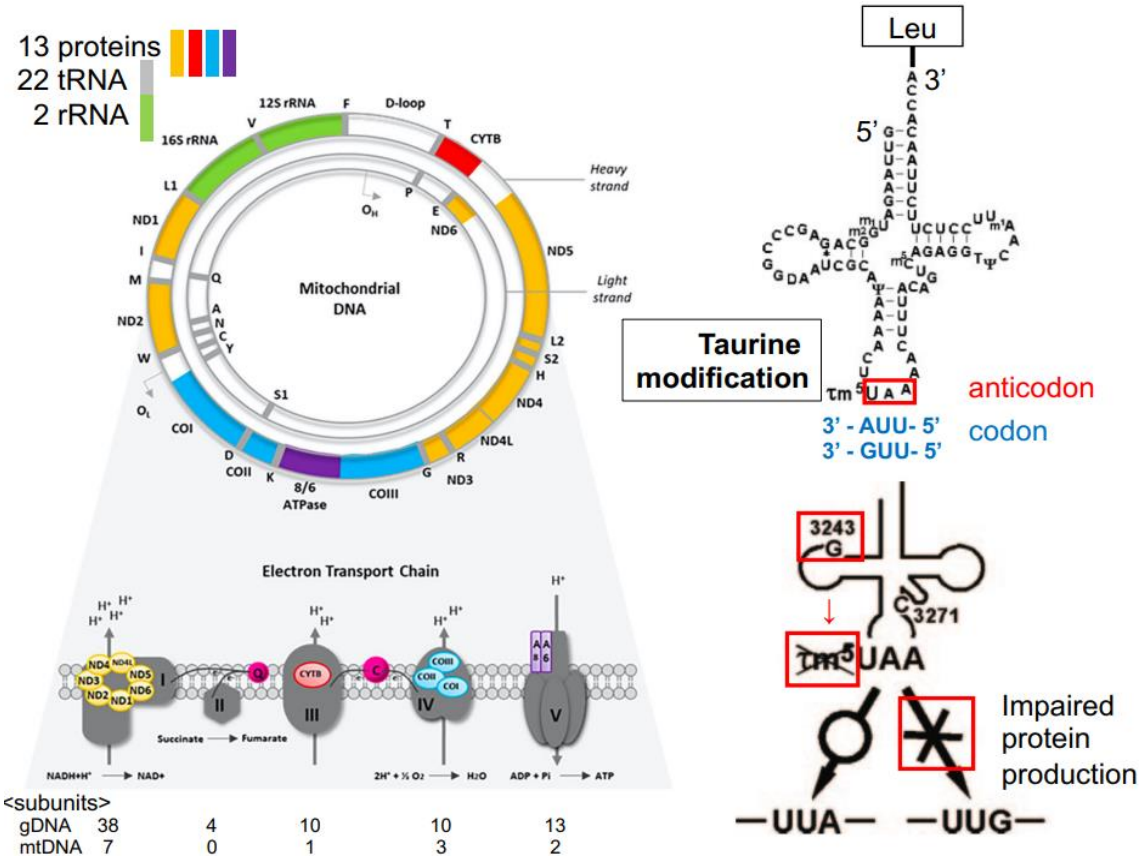
Management of this disease is **mainly symptomatic**.

Supportive treatment includes adequate fluid, nutrition, and medication and anti-psychotic or sedative therapy, as well as rehabilitation

1. Epileptic seizures should be aggressively treated because neurons utilize glycogen as an ATP source during epileptic activity.
2. Remember on mitochondrial toxicity associated with valproic acid, carbamazepine, phenytoin, and phenobarbital. Metformin is contraindicated in patients with MD, especially MELAS and diabetes, due to the predisposition for lactic acidosis
3. Aerobic training
4. Mitochondrial replacement therapy ongoing

Treatment approaches [36]

Taurine modification as a treatment approach for 3243A>G, 3271T>G, 3244G>A, 3258T>C or 3291T>C mutations



Pic.11.8.

Leigh syndrome[36]

Leigh syndrome is thought to affect about 1 in 40,000 births.

Characterized by necrotizing lesions of the basal ganglia, cerebellum, diencephalon, and/or brainstem, leading to a progressive decline of neurological function.

The clinical hallmarks include psychomotor delay or regression, hypotonia, tremor, weakness, truncal ataxia, and lactic acidosis. Dystonia is often associated with Leigh syndrome too

The typical clinical onset occurs in the first 2 years and patients die at about 3 years of age. Delayed development is the first manifestation in most patients. Motor weakness and ataxia may be more common in children with onset after 2 years, with a less severe clinical course.

MERRF: Mitochondrial Encephalopathy with Ragged Red Fibers [36]

The syndrome characterized by seizures, myoclonus, and ataxia

A mitochondrial syndrome where myoclonus is the prominent clinical feature, and which does not meet the criteria of other well-defined mitochondrial encephalopathic syndromes, including MELAS, Leigh, and Alpers syndromes.

Ataxia is a specifically associated feature, differently from epileptic seizures.

Some practical recommendations[35]

	Age	Dosage	Route
Vit B1	<3years >3 years adults	150 mg/day 300 mg/day 900 mg/day	Per os
Vit B2		50 -400 mg/day	Per os
Vit B3 (niacin)		10 mg/kg/day	Per os
Vit B7 (biotin)		2-10 mg/kg/day	Per os
Vit B9 (folate)		1,5- 5 mg/kg/day	Per os
Vit B12		1000 mg/day	Per os
Vit E		2-10 mg/day	Per os
Coenzyme Q10	children adults	2-8 mg/kg/day 50-600 mg/day	Per os
Nacetylcysteine		10 mg/kg/day	Per os
Vit C		25 mg/kg/ day	Per os
Levocarnitine		100 mg/kg/day	Per os
Creatine	adults children	5 g/day 0,1 g/kg/day	Per os
L-arginine	children adults	0,5 g/kg 10 g/m² body surface	iv

Table 11.5.

Summary

A non-invasive, bigenomic (nDNA and mtDNA) sequencing approach (using both whole-exome sequencing and optimized mtDNA analysis to include large deletions) could be **the first step in investigating mitochondrial disorders**.

Muscular biopsy need to be provided in order to distinguish a type of mitochondrial diseases (COX reaction of RRFs).

2/3 mutations are **single large deletions** and these are **de novo mutations** and **not inherited** BUT 1/3 mutations are **point mutations** (m.3243A>G and others) and **maternal inherited**. **Genetic family consultation** must be provided!

Gene mutation specific therapy is available – **taurine modification** therapy

Case 12. Myopathy: from DMD to LGMD

Description of the case of 6y8m boy

Chief complaint: Muscle weakness with high CK

Past medical history: negative

Family history: no neuromuscular disease, no consanguinity

Physical examination: he had mild proximal muscle weakness with positive Gowers sing. No muscle atrophy was seen. Calf muscle were hypertrophic. Facial muscle was also spared. Mild ankle joint contracture was seen.

Laboratory data: CK 24.880 IU/L(normal:62-287)

Muscle MRI: fat infiltration in gluteus maximus and medius muscles

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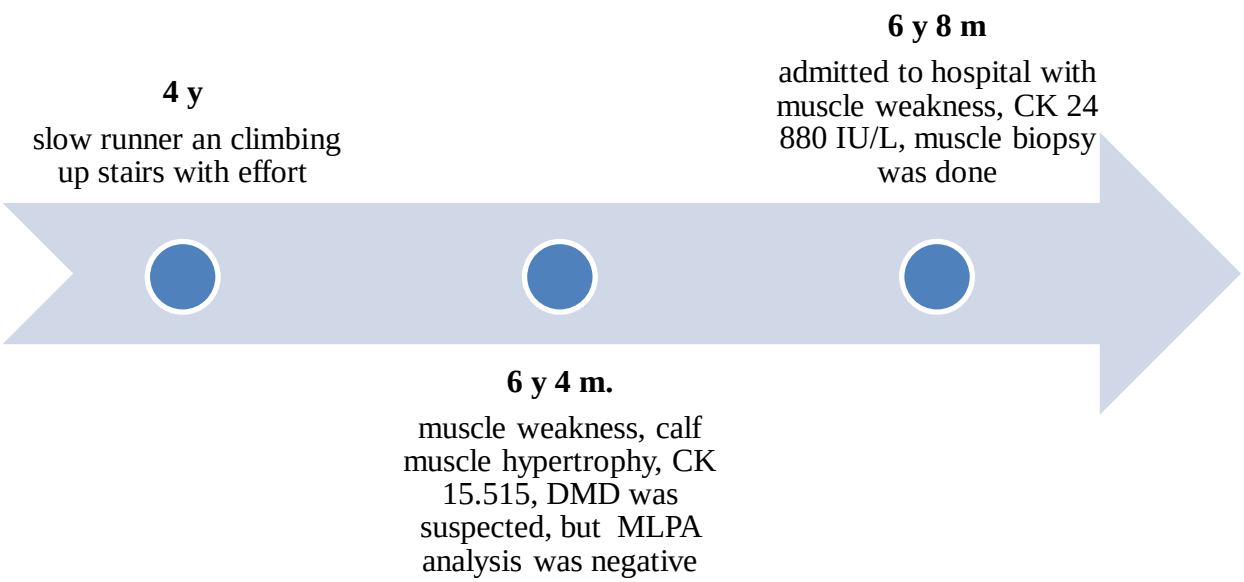
History of the illness



Key findings at this stage of assessment

Boy , 6 y.8 m;

Early development was normal until 4 year of age.

At the age of 4 years- slow runner, difficulty to climb up stairs.

At 6 y4 m: muscle weakness progressed, CK 15.515 UI/L , calf hypertrophy, MLPA on DMD was negative.

At 6 y.8 m: muscle weakness, CK 24.880 IU/L, Gowers' sign, calf hypertrophy, mild ankle contracture.

On MRI: fat infiltration of gluteus maximus and medium muscles

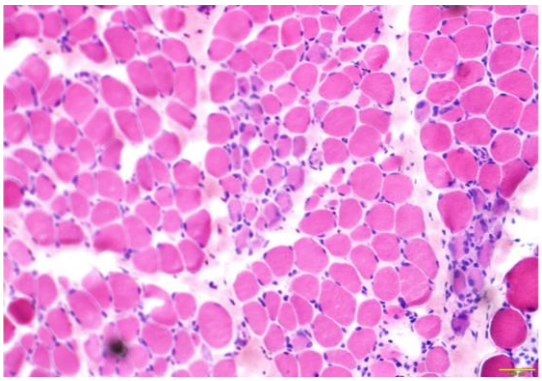
We can still suspect and need to rule out DMD as point mutation is still possible at DMD gene and muscle biopsy was provided

What other diagnosis is possible?

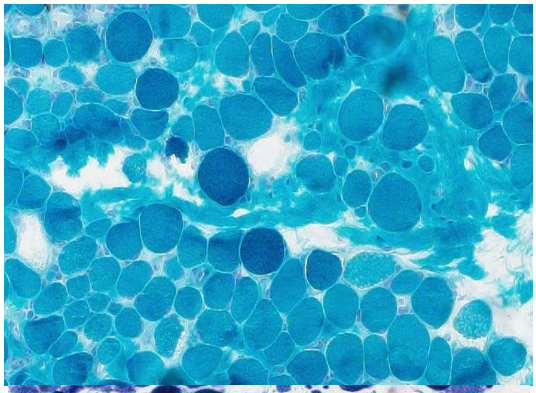
CK – 24 880 IU/L , which is a very high and suggests to muscle dystrophy**:**

1. DMD (boys)
2. Sarcoglicanopathy (boys or girls)
3. Calpainopathy (boys and girls)
4. Pompe disease (boys and girls)
5. Inflammatory myopathies (dermatomyositis, immune-mediated necrotizing myopathy (IMNM) (boys or girls)

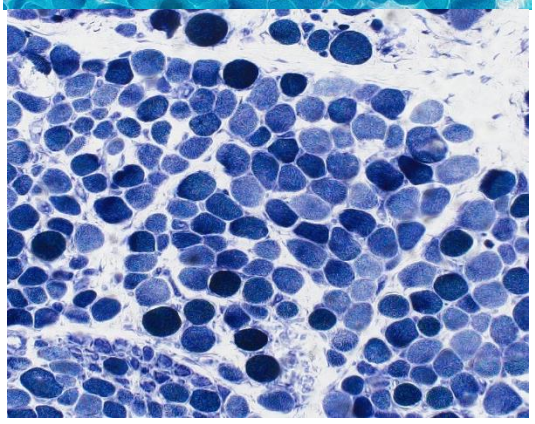
Muscle biopsy data (Pic.12)



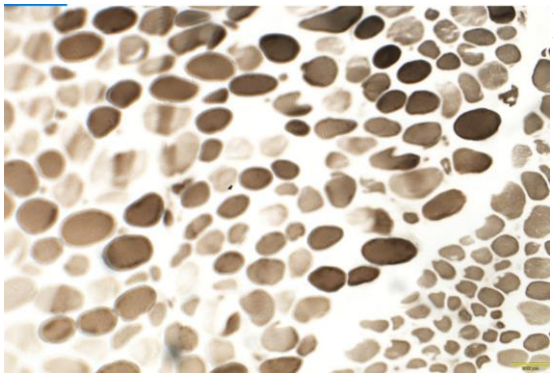
Pic.12.1. On H&E staining: moderate variation in fiber size from 10 to 50 microns in diameter. A few necrotic and some regenerating fibers are seen. Mild endomysia fibrosis.
Clusters grouping of regenerating fibers, which is a sign of chronic necrotic- regeneration condition (myopathic sign**)**



Pic.12.2. On mGT, ragged-red fibers (RRFs), nemaline rods, and rimmed vacuoles are not seen



Pic.12.3. On NADH-TR, intermyofibrillar networks are well-organized except in regenerating fibers

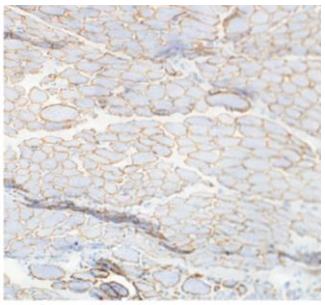


Pic.12.4. On ATPase, fiber type grouping is not seen. Type 2C fibers scattered

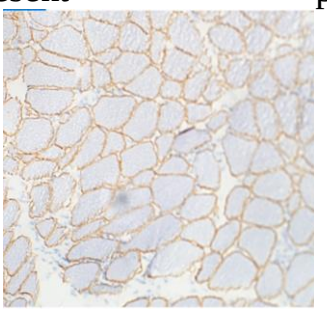
Remarks: Muscle fiber types functions:
Type 1 fibers – posture
Type 2 fibers – actions

Immunohistochemistry

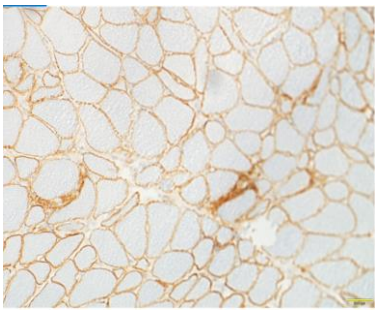
DYS 1(rod) is present

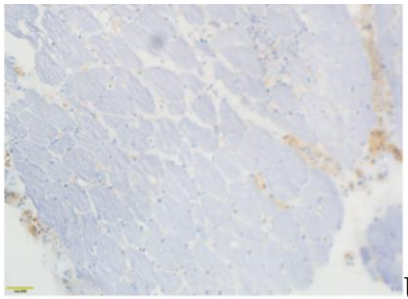


DYS 2(C-terminal) is present

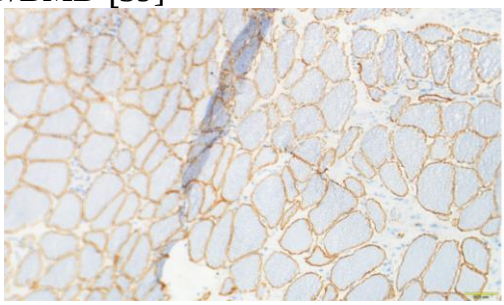


DYS 3(N-terminal) is present

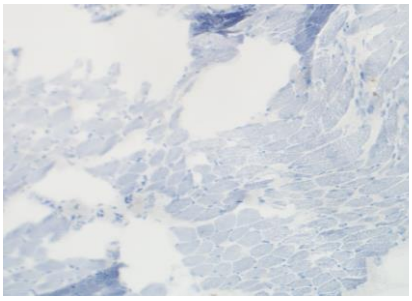




Utrophin expression is absent which is excluded DMD/BMD [39]



Example of normal expression of **α** SG sarcoglican



The examined boy has no expression of α- sarcoglican

Pic.12.5.

PATHOLOGICAL DIAGNOSIS:

Myopathic change with:

1. Variation in fiber size, moderate
2. Regenerating fibers and necrotic fibers, some
3. Type 2C fibers, scattered

COMMENTS:

The above findings are suggestive of muscular dystrophy. Final diagnosis is pending on IHC.

According to IHC findings on absent of sarcoglycan A possible to suggest on sarcoglycanopathy

Literature overview [40]

The sarcoglycan complex is comprised of a-sarcoglycan (previously termed adhalin and 50 DAG), b-sarcoglycan (A3b), d-sarcoglycan, and e-sarcoglycan.

Alpha-sarcoglycan and g-sarcoglycan have been found to be present only in skeletal and cardiac muscle by immuno-blotting (Yamamoto et al., 1994) whereas b-, d- and e-sarcoglycan are ubiquitously distributed (Ettinger etal., 1997; McNally et al., 1998).

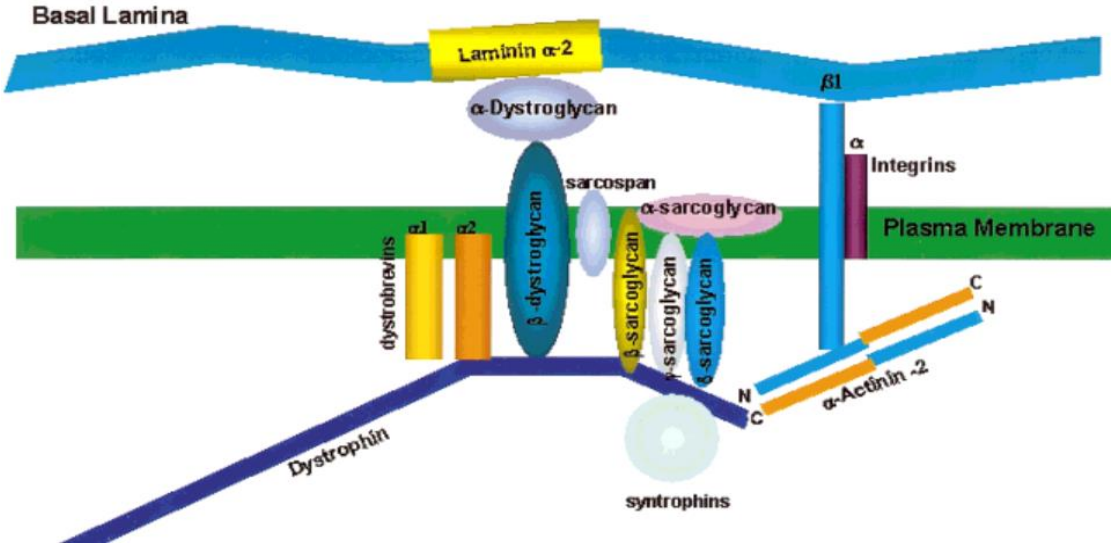
We have been able to identify many of the components of the muscle fiber cytoskeleton, but still, we have little idea of the true function of each member of the complex.

The phenotypes of sarcoglycanopathies are rather, similar to dystrophinopathies (DMD/BMD), except for the absence of cognitive dysfunction and more frequent occurrence of scapular winging [41].

The most common presentation is a DMD-like phenotype with onset of weakness in childhood (especially in LGMD2C/R5, LGMD2E/R4, LGMD2F/R6), and the disease is more severe and rapid than in other LGMDs.

Most patients have a severe and rapid course, leading to loss of independent walking ability before age 30-40 years.

Schematic representation of dystrophin and the dystrophin-associated[21]

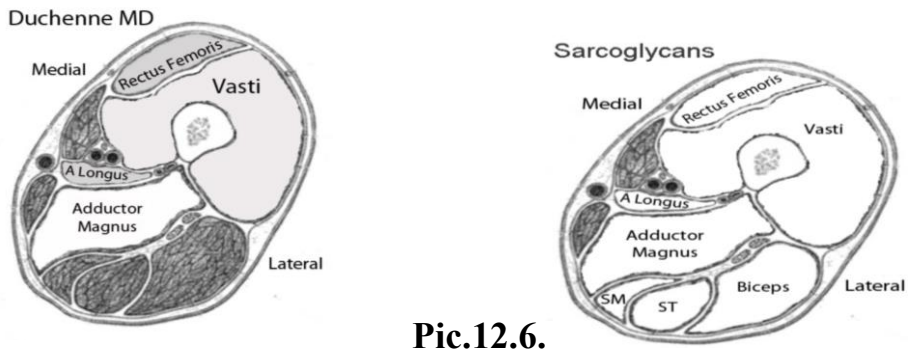


Scheme 12.1

Proposed diagnostic algorithm for myopathies [42]

1. Neurological examination
2. Hypothyroidism should be excluded - plasma TSH, free T3, free T4
3. Lactic acid and plasma acylcarnitine should be measured for exclusions of mitochondrial and inborn errors of metabolism such as fatty acids metabolic disorders.
4. Dried blood spot for GAA enzyme test to rule out Pompe disease
5. Muscle MRI for distinguish inflammatory myopathies (dermatomyositis and IMNM), specific antibodies should be checked
6. For diagnosis of hereditary myopathies genetic analysis (MLPA, WES) and muscle biopsy should be provided

MRI findings [43]



Pic.12.6.

DMD	LGMD/sarcoglicanopathy

At the age of 5 yo- gluteus maximus is involved	The most and earliest affected muscles were the thigh adductors, glutei and posterior thigh groups and the iliopsoas is typically early spared.
At the age of 6-7 yo – rectus femoris and vastus	Another important finding was the sparing of the medial part of the adductor longus.
Later stage – gastrocnemius is involving	The lower leg muscles were relatively spared until loss of ambulation occurred.
	Also, even in advanced disease, the tibialis posterior and flexor digitorum longus are spared.

Scheme 12.2

Summary

Sarcoglycanopathies are the most severe forms of autosomal recessive limb-girdle muscular dystrophies (LGMDs), constituting about 10–25% of LGMDs.

The **clinical phenotype is variable**, but onset is usually in the **first decade of life**.

Four subtypes are known: LGMDR3, LGMDR4, LGMDR5 and LGMDR6, caused, respectively, by mutations in the **SGCA, SGCB, SGCG and SGCD genes**.

Many **different mutations** have already been **identified** in all the sarcoglycan genes, with **a predominance** of some mutations in **different populations**.

The diagnosis is currently **based** on the **molecular screening** for these mutations.

Therapeutic approaches include the strategy of gene replacement mediated by a vector derived from adeno-associated virus (AAV).

Therapeutic trials in humans are ongoing

Case 13. Neurogenic case

Description of the case of 44 y, female

Chief complaint: Drop foot

Past medical history: negative

Family history: father, parental grandmother has gait disturbance (no detailed info available)

Physical examination: she showed steppage gait but also Gowers' sign. She had marked predominantly distal muscle weakness and atrophy, sparing facial muscles. Sensation was normal except that vibration sensation was mildly decreased at distal legs. DTRs were all absent.

Laboratory data: CK: 395 IU/L

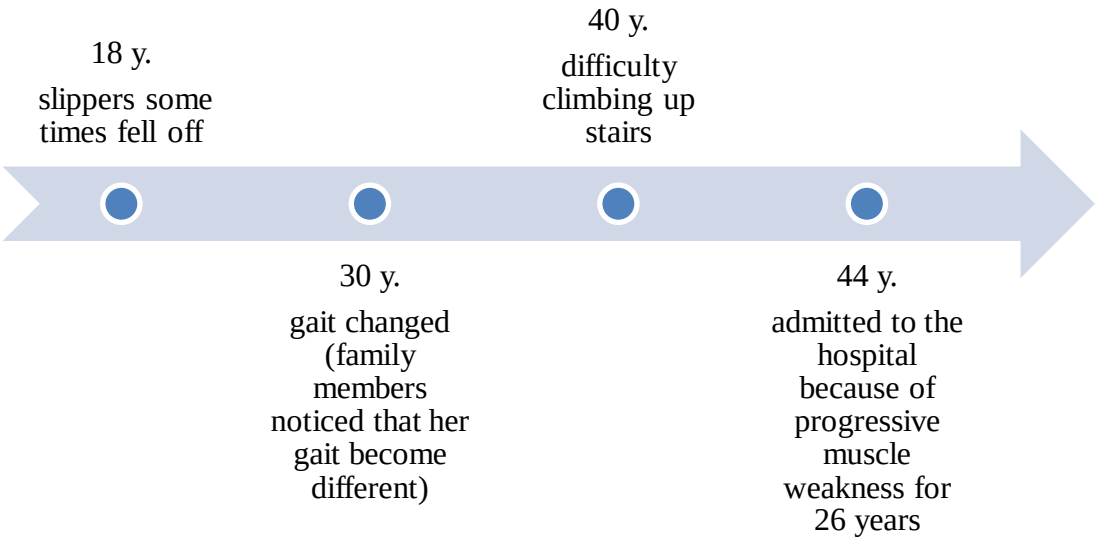
EMG: denervation potentials. SNAP (sensory nerve action potential) * not elicited. CMAP (compound of muscle action potential) ** decreased

ECG: normal

*-during electrophysiological examinations there is a decrease in amplitude of the sensory nerve action potential (SNAP) resulting from nerve damage at or distal to the dorsal root ganglion.

-Reduction of CMAP amplitude reflects **loss of motor axons and, therefore, is directly relevant to ALS and SMA. Median nerve CMAP values decline substantially in ALS patients (Shefner et al., 2011). Despite the simplicity and attractiveness of CMAP recording, it varies with stimulus intensity, electrode position, limb position, and temperature.

History of the illness



Key findings for this step

Suspicion **on autosomal dominant condition** (father, grandmother)

Onset of the disease: 18-year, slow progression of muscle weakness

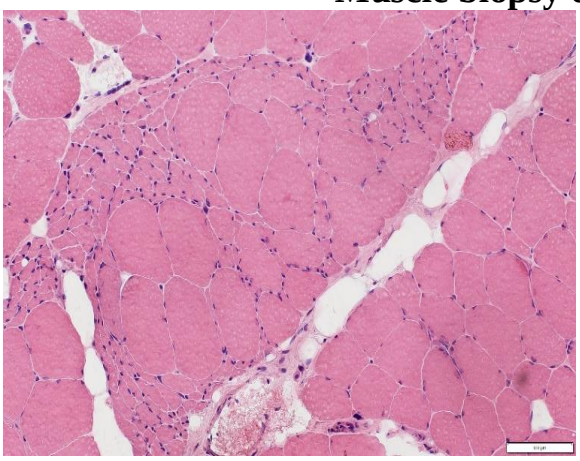
Drop foot, steppage gait, Gowers' sign, marked predominantly distal muscle weakness and atrophy, sparing facial muscles. Normal sensation

except that vibration sensation was mildly decreased at distal legs. DTRs were all absent. Mildly elevated CK (395 IU/L)

Neurogenic EMG: denervation potentials. SNAP (sensory nerve action potential) not elicited. CMAP (compound of muscle action potential) decreased

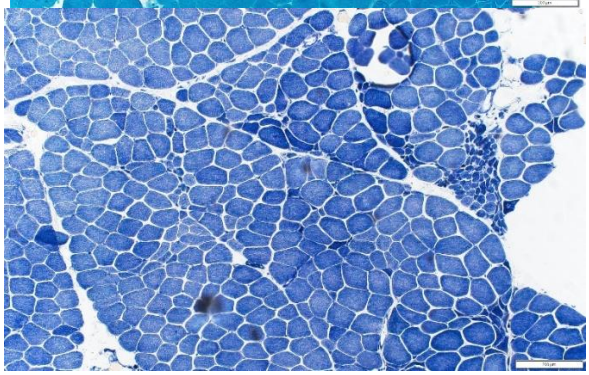
ECG: normal

Muscle biopsy data (Pic.13)

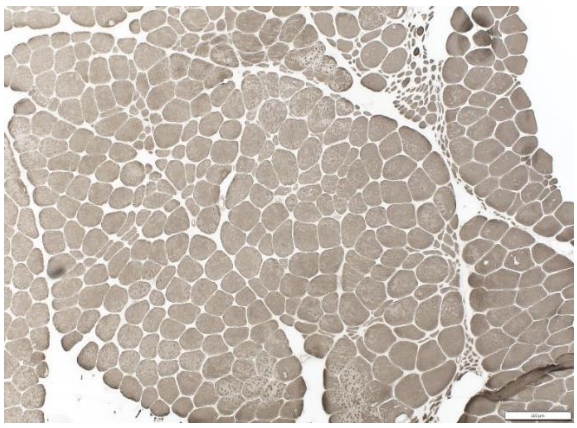


Pic.13.1. On H&E: there is bimodal distribution in fiber size and fibers size measuring from a few to 10 microns in smaller group and from 66 to 77 microns in diameter in larger group. There are no necrotic and regenerating fibers. Small angular fibers are clustered in part showing small group atrophy. No endomysial fibrosis is seen. No lymphatic infiltration is seen. There are few fibers with internalized nuclei.

Pic.13.2. On mGT, there is no fibers with rimmed vacuoles (RVs), ragged red fiber (RRF) and nemaline bodies. In the present specimen, peripheral nerve bundles are not included



Pic.13.3. On NADH-TR, intermyofibrillar networks are well organized .



Pic.13.4. On ATPase, fiber type grouping is seen. Some type 2C fibers are seen

Pathological diagnosis

Neuropathic change with:

1) variation in fiber size, bimodal
2) small group atrophy
3) fiber type grouping
4)fibers with internalized nuclei, a few
5) type 2 C fibers, some

pathognomonic for denervation and reinnervation process

Comments: the above findings reflect mild denervating and re-innervating process.

Neurogenic disease should be confirmed
Why is important provide a biopsy?

Neurogenic means involving the motor neurons or the peripheral nerve.

It is rarely possible to precisely define the disorder from a muscle biopsy, but there are certain suggestive patterns.

Careful clinical and electrophysiological investigations often give a clue to the defective gene and muscle biopsies are now performed less often in neurogenic disorders.

However, some neurogenic atrophies, may mimic some muscular dystrophies or myopathies, such as distal myopathies. In such cases muscle pathology can be useful in differential diagnosis

Overview of the literature [21,44,45,46]

Neurogenic disorders
(inherited and acquired clinical disorders caused by a defect in upper or lower motor neurons of the peripheral nerve):

Amyotrophic lateral sclerosis (ALS; upper and lower motor neurons);

Hereditary motor and sensory neuropathies (HMSN; motor and sensory neurons and peripheral nerves);

The spinal muscular atrophies (SMA; lower motor neurons)

Inflammatory peripheral neuropathies

Aging of muscles and some metabolic condition are accompanied by a neuropathy/denervation

General pathological features of denervated muscle

Denervated muscle fibers shrink in size

In chronic condition such as ALS the atrophic fibers have an angular shape, in contrast to the rounded shape of the atrophic fibers in SMA.

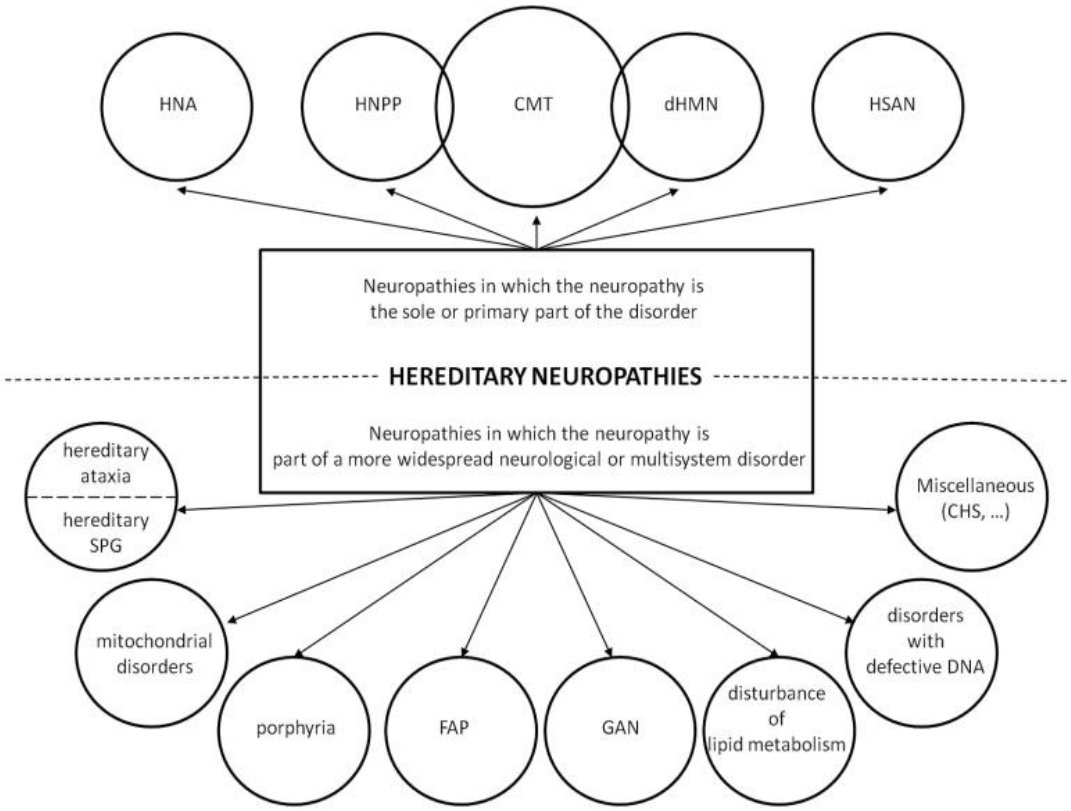
One motor nerve supplies many muscle fibers, denervation will result in atrophic fibers scattered at random in a biopsy. That is why two populations of muscle fibers are seen in denervated muscle: atrophic ones that are denervated and those that are relatively normal in size or hypertrophied. The presence of this biomodal or twin-peaked configuration calls “fiber types groping” and is pathognomonic of denervation

Neurogenic disorders

Condition	Type of the disorder	Localization of defect	Cause	Key diagnostical approach
Amyotrophic lateral sclerosis	Inherited	upper and lower motor neurons	SOD1, FUS, ALS2, SETX, VAPB,TDP-43,TARDPB, VCP, OPTN, ANG gene's mutations	NGS
Hereditary motor and sensory neuropathies	Inherited	motor and sensory neurons and peripheral nerves	Genes (http://www.molgen.ua.ac.be/cmtmutations/	EMG(n.suralis), NGS
SMA	Inherited	Lower motor neuron	SMN 1 and SMN 2, IGHMBP2, MEGF10,	MLPA, NGS
Inflammatory peripheral neuropathies	Acquired	Peripheral nerves	inflammation	LP, EMG
Aging and metabolic	association with underlying conditions, and as consequences of aging	Peripheral nerves	Metabolic, aging, malignancy, amyloidosis	Lab analysis (metaboloc), muscle biopsy, EMG

Table 13.1.

Classification of Hereditary neuropathies



Scheme 13.1.

Charcot–Marie–Tooth (CMT) disease, the most frequent form of inherited neuropathy, is a genetically heterogeneous group of disorders of the peripheral nervous system, but with a quite homogeneous clinical phenotype: [44]

1. progressive distal muscle weakness and atrophy,
2. foot deformities,
3. distal sensory loss
4. decreased tendon reflexes.

Characteristic (clinical, biological and radiological) sings of CMT with correspondence with possible mutations

Phenotype characteristics	Subtypes of CMT
Abnormal brain MRI (white matter abnormalities)	XL-CMT-*GJB1*; AR-CMTde-*NDRG1*; AD-CMTin-*INF2*; AD-CMTax-*MFN2*
Pyramidal tract involvement	AD-CMTax-*MFN2*; AR-CMTax-*GDAP1*; XL-CMT1, AD-dHMN-*BSCL2;* AD-dHMN-*REEP1;* AD-dHMN-*SETX; AD-dHMN-DYNC1H1;* AD-dHMN-*BICD2*; AD-CMTax-*NEFL;* AR-CMTax-*C12ORF65*; AD-CMTax-*KIF5A*; AD-CMTax-*mtATP6*
Mental retardation	X-CMT-Unknown; XL-CMT-*AIFM1*
Deafness	AD-CMTde-*MPZ*; AD-CMTde-*PMP22*; AD-CMTde-*NEFL*; AD-CMTax-*MPZ*; X-CMT-*GJB1*; X-CMT-*AIFM1*; XL-CMT-*PRPS1*; AR-CMTde-MTMR2; AR-CMTde-*NDRG1*; AR-CMTde-*SH3TC2*
Optic neuritis	AD-CMTax-*MFN2*; AD-CMTde-*PMP22dup*
Optic atrophy	AD-CMTax-*MFN2*; XL-CMT-*PRPS1*; XL-CMT-*AIFM*; AR-CMTax-*C12ORF65*; XL-CMT-*PRPS1*
Pupillar abnormalities	AD-CMTde-*MPZ*; AD-CMTax-*MPZ*
Glaucoma	AR-CMTde-*SBF2*
Cataract	AR-CMTde-*CTDP1*; AR-CMTax-*DNM2*; AD-CMTin-*DNM2*
Lancinating pain	AR-CMTde-*SBF2*; AD-CMTax-*RAB7*; AD-CMTax-*MPZ*
Steroid responsive neuropathy	AD-CMTde-*MPZ*
Diaphragm and vocal cord palsy	AD-CMTax-*TRPV4*; AR-CMTax-*GDAP1*; AD-CMTax-*GDAP1*; AD-CMTax-*MPZ*; AR-CMTde-*GDAP1*; AR-CMTde-*MTMR2*; AD-CMTax-*MFN2;* X-dHMN-*LAS1L; AR*-dHMN-*IGHMBP2*
Proximal muscle involvement	AD-CMTax-Unknown; AD-CMTax-*LRSAM1*; AR-CMTax-*LMNA*
Predominantly upper limbs involvement	AD-CMTax-*GARS*; AD-CMTax-*HSPB8*; AD-dHMN-*TFG;* AD-dHMN-*BSCL2*
Sensory anomalies and ulcerations	AD-CMTax-*RAB7*
Severe deformations, scoliosis	AR-CMTde-*SH3TC2*; AR-CMTde-*FGD4*; AR-CMTde-*PRX*; DSS; AD-CMTax-*GARS*; AD-CMTax-*GDAP1*; AD-CMTax-*HSPB8*
HyperCKemia, hyperlipemia, diabetes	AD-CMTax-Unknown; AD-dHMN-*TFG*; AD-CMTax-*NEFL*
Neutropenia	AD-CMTin-*DNM2*
Focal segmental glomerulosclerosis	AD-CMTin-*INF2*
Skin hyperelasticity, age-related macular degeneration	AD-CMTde-*FBLN5*

AD, autosomal dominant; AR, autosomal recessive; CMT, Charcot–Marie–Tooth; dHMN, distal hereditary motor neuropathies; DSS, Dejerine–Sottas syndrome; LMNA, lamin A/C.

Table 13.2.

Amyotrophic lateral sclerosis (ALS)[45]

It is a fatal motor neuron disease characterized by degenerative changes in both upper and lower motor neurons (Rowland and Shneider, 2001).

Onset typically occurs in late middle life and presents as a relentlessly progressive muscle atrophy and weakness, with the effects on respiratory muscles limiting survival to 2–4 years after disease onset in most cases (Chio et al., 2009).

ALS is the most common adult motor neuron disease with an incidence of 2 per 100,000 and prevalence of 5.4 per 100,000 individuals (Chiò et al., 2013).

Current treatment options are based on symptom management and respiratory support with the only approved medications in widespread use, Riluzole and Edaravone, providing only modest benefits and only in some patients (Petrov et al., 2017; Sawada, 2017).

Many factors have contributed to the slow progress in developing effective treatments for this devastating disease

Up to 10% of ALS affected individuals have at least one other affected family member and are defined as having familial ALS (fALS);

almost all of these cases have been found to be inherited in an autosomal dominant manner (Kirby et al., 2016).

The remaining 90–95% of ALS cases occur in people with no prior family history;

these individuals are said to have sporadic ALS (sALS) (Chen et al., 2013)

Proportion of ALS explained by the four most commonly mutated genes in Asian and European populations.
Data adapted from Zou et al. (2017)

Scheme 13.2.

Spinal muscular atrophy (SMA) [46]

The disease is caused by autosomal recessive mutations of the SMN1 gene and is characterized by loss of motoneurons and progressive muscle weakness.

The birth incidence of SMA is around 1 in 10,000 and it is thus classified as an orphan disease.

Disease severity covers a broad spectrum and onset ranges from neonatal period to adulthood, while onset in the first years of live is most common [1].

Approved a disease modifying therapy with three drugs: nusinersen (antisense oligonucleotide), onasemnogen abeparvovek (gene replacement therapy) and risdiplam (small molecule)

Summary of typical features of Spinal muscular atrophy types

Features	Type 1	Type 2	Type 3
Onset	In utero or within fist few months of life	Between 6 and 12 months	From second year of life
Clinical features	Severe hypotonia, muscle weakness, poor head control, bell-shaped chest, intercostal weakness, diaphragmatic breathing, sucking difficulties, weak cry	Hypotonia, symmetrical, proximal weakness, fasciculation of tongue, tremor of hands, DTR low or absent, joint laxity, scoliosis, respiratory problems	Weakness static or may be progressive, difficulty running, jumping and climbing stairs, waddling gait, flat footed, Gowers' manoeuvre, hand tremor, tongue fasciculation(variable), joint laxity
Motor ability	Sitting and weight-bearing never achieved	Able to sit, unable to stand unaided or walk	Able to walk but may be limited
Investigations	CK normal, EMG features of denervation MLPA	CK normal or mildly elevated, EMG features of denervation MLPA	CK normal or moderately elevated EMG features of denervation MLPA
Muscle pathology	Large groups of atrophic fibers, fiber type grouping, hypertrophic type 1 fibers, atrophy of both fiber types	Large groups of atrophic fibers, fiber type grouping, hypertrophic type 1 fibers	Variable, minimal change or small groups of atrophic fibers, fiber type grouping with normal size or hypertrophic type 1 fibers, architectural changes- whorls, cores, splits. May be difficult to distinguish from LGMD
Prognosis	Life threatening condition, die before 2 years	Non - progressive in most cases prognosis is good	Some cases are improve within time, probably as a result of compensating reinnervation of muscles and supportive care
NOTICE!	Cardiac, facial and cranial, diaphragmatic muscles are spared		

Table 13.3.

Summary

Neurogenic diseases are a heterogeneous group of neuropathies with neurons or peripheral nerves involvement.

An accurate diagnosis is not always easy, but genetic analysis may be orientated by electro-clinical, biological and sometimes pathological signs (with sometimes specific signs function of the genes)

Case 14. DMD carrier case

Description of the case of 10 y.o, girl

Chief Complaint: muscle weakness and myalgia after exercises

Family History: none

Past History: none

Medication: none

Present Illness: Early development is not remarkable. She was normal until 8 y.o. After age of 8 y had difficulty in climbing up stairs and need hand rails, and also had myalgia after exercises. From the age of 9y hypertrophy of calf muscles was noted. She visited hospital 3 months ago and the grip strength was very low.

Neurological Examination muscle weakness predominantly in proximal group of muscles,

Gowers' sign is positive,

waddling gait,

DTR is normal,

myalgia in thigh after exercises

hypertrophy in calf muscles.

Intelligence is low (IQ, DQ is 62).

Laboratory Examination: CK 10936 U/L, aldolase is elevated up to 80,7; AST 183, and ALT 317, lactate 22,6 (normal 4,4-17,0) pyruvate acid 1,0 (0,3-0,9)

Muscle MRI: fat infiltration in thigh (quadriceps femoral and vastus lateralis) and gluteus maximus and medius, also gastrocnemius, symmetrical, more thigh than calf muscles.

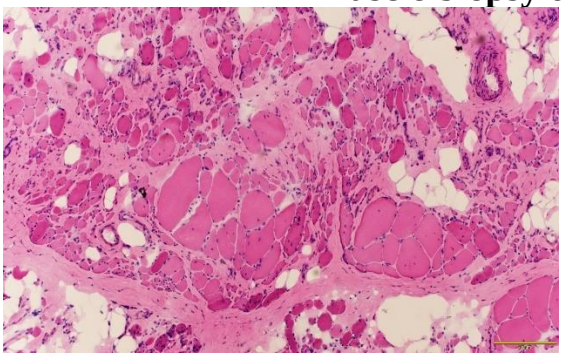
Differential diagnosis

#1. LGMD like sarcoglicanopathy, dystroglycanopathy

#2. DMD career

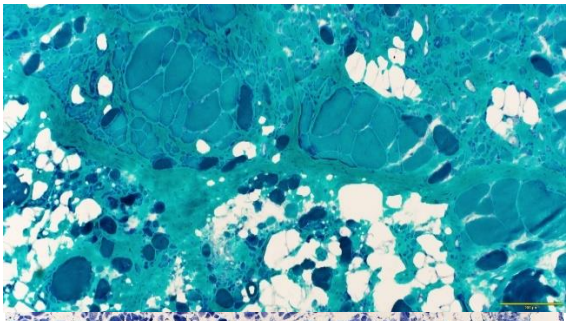
#3. IMNM

Muscle biopsy data (Pic.14)

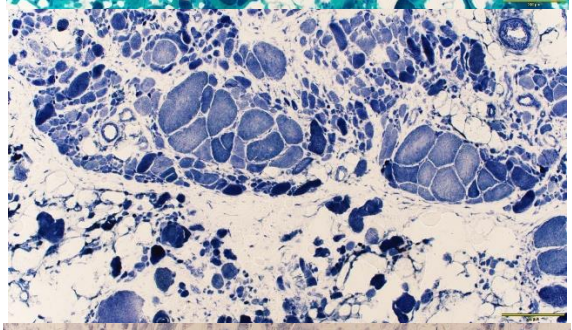


Pic.14.1. H&E: there is a marked variation in fiber size ranging from a few to 170 microns in diameter. In some fascicles, majority of muscle fibers are replaced by adipose tissue while other areas exhibit some fascicles that appear to have most of the fibers spared.

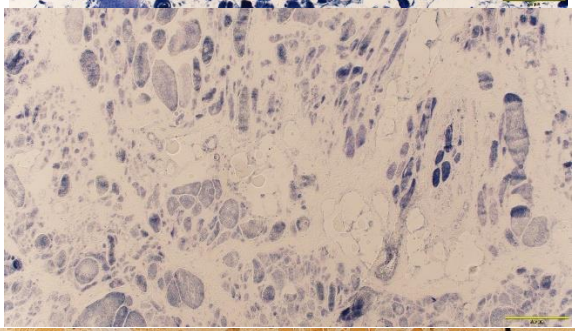
Although, fiber size variation is still present in the relatively spared fascicles. A few necrotic but scattered regenerative fibers are seen. Fibers with internalized nuclei are scattered. The degree of endomysial fibrosis is variable depending on the fascicles, with some fascicles having marked fibrosis. There is no apparent mononuclear cell infiltration. Perifascicular atrophy is not seen.



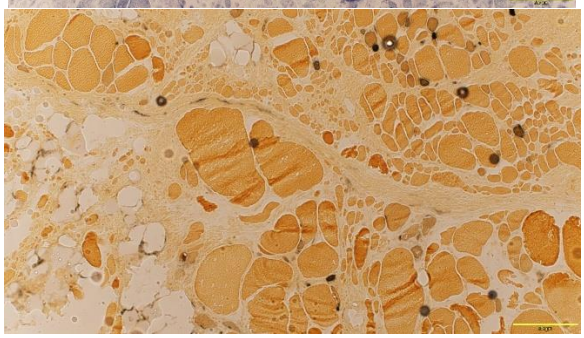
Pic.14.2. mGT: there are no RRFs, rimmed vacuoles, or nemaline rods seen. The peripheral nerve is well myelinated



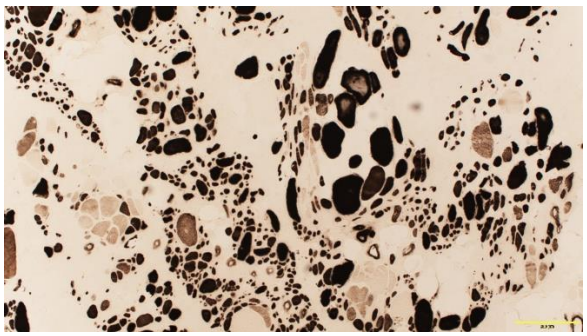
Pic.14.3. NADH-TR, intermyofibrillar networks are moderately to marked disorganized in scattered fibers



Pic.14.4. SDH, strongly SDH-reactive blood vessels(SSVs) are not highlighted

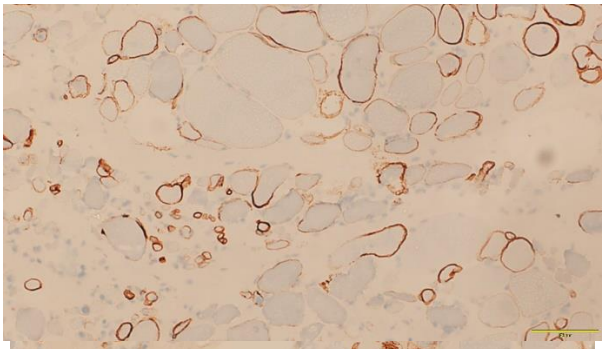


Pic.14.5. ALP, enzymatic activity is not seen in the perimysium

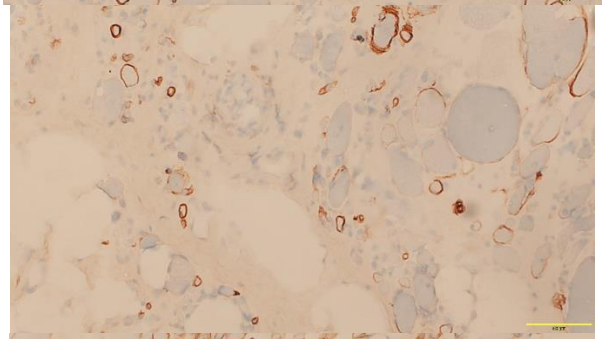


Pic.14.6. ATPase: fiber size variation is seen in both Type 1 and Type 2 fibers. Type 2C fibers are scattered

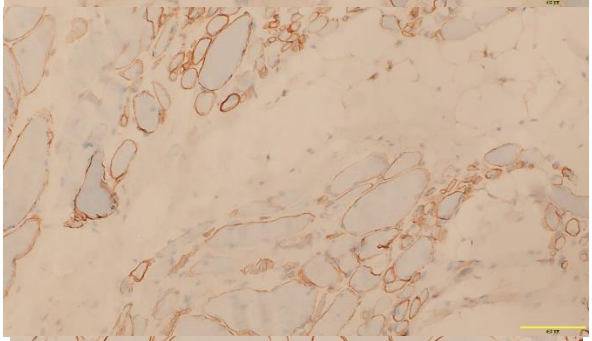
Immunohistochemistry



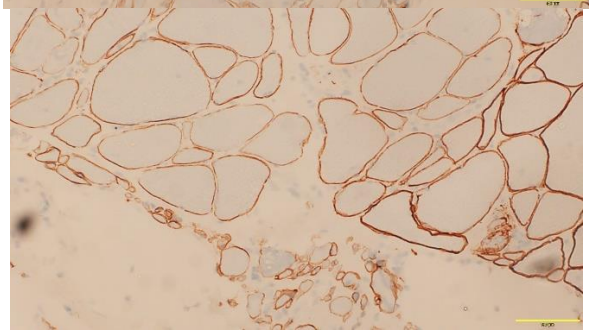
Pic.14.7. Dys 1 mosaic



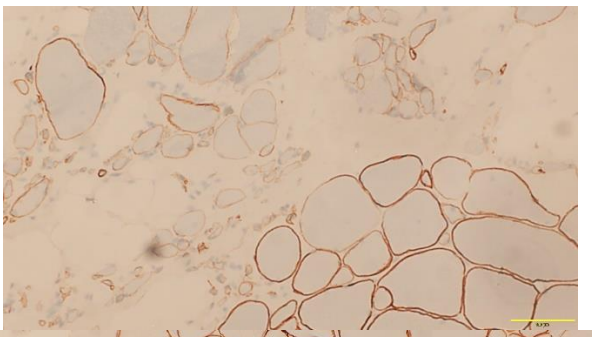
Pic.14.8. Dys 3 mosaic



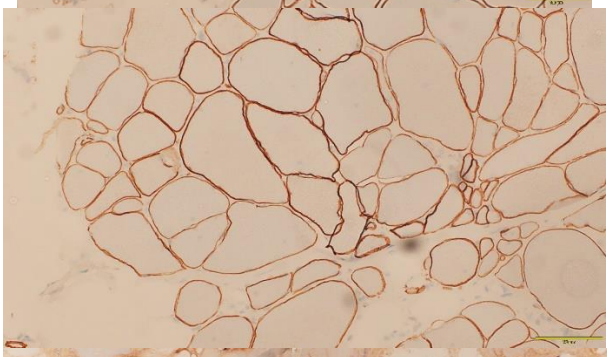
Pic.14.9. Utrophin positive



Pic.14.10. Alpha-SG faint in part

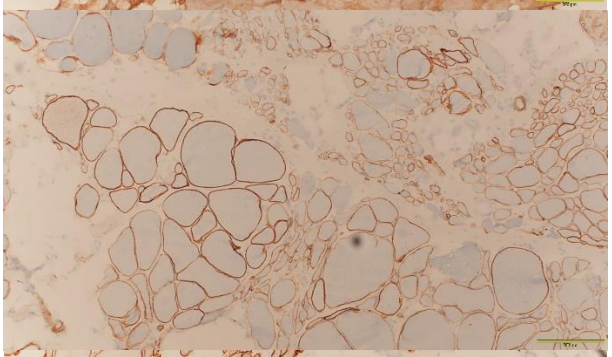


Pic.14.11. Beta-SG mosaic

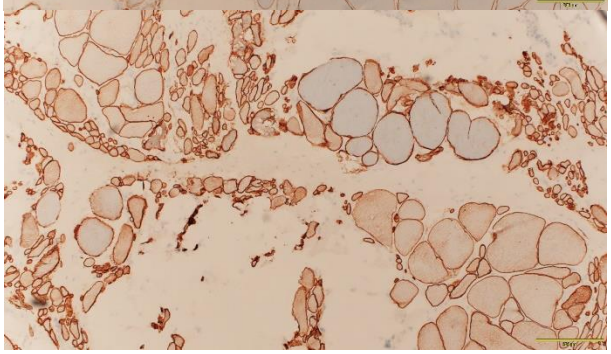


Pic.14.12. Gamma SG positive

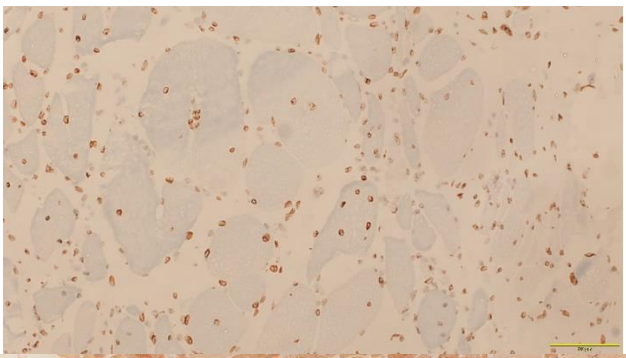
Pic.14.13. Alpha- DS faint



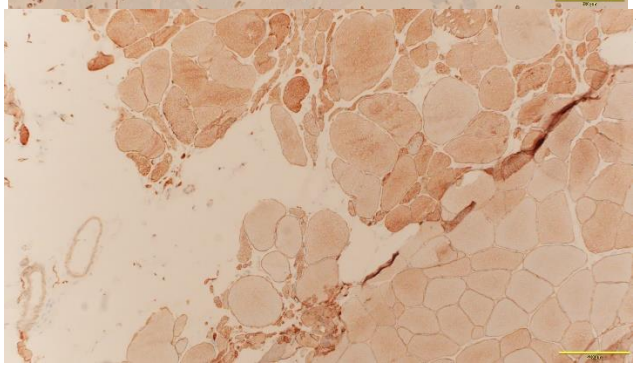
Pic.14.14. Beta-DS positive



Pic.14.15. Caveolin 3 positive



Pic.14.16. Emerin positive



Pic.14.17. Dysferlin positive

Conclusion for diagnosis of this case
DMD carrier
Muscle weakness
High CK
Gluteus maximus, medius, calf
Dytrophin mosaic
Utrophin positive
Recommended: Cardiac follow-up, Genetic/ family consultation

Main clinical features of DMD and BMD
The cause of DMD/BMD

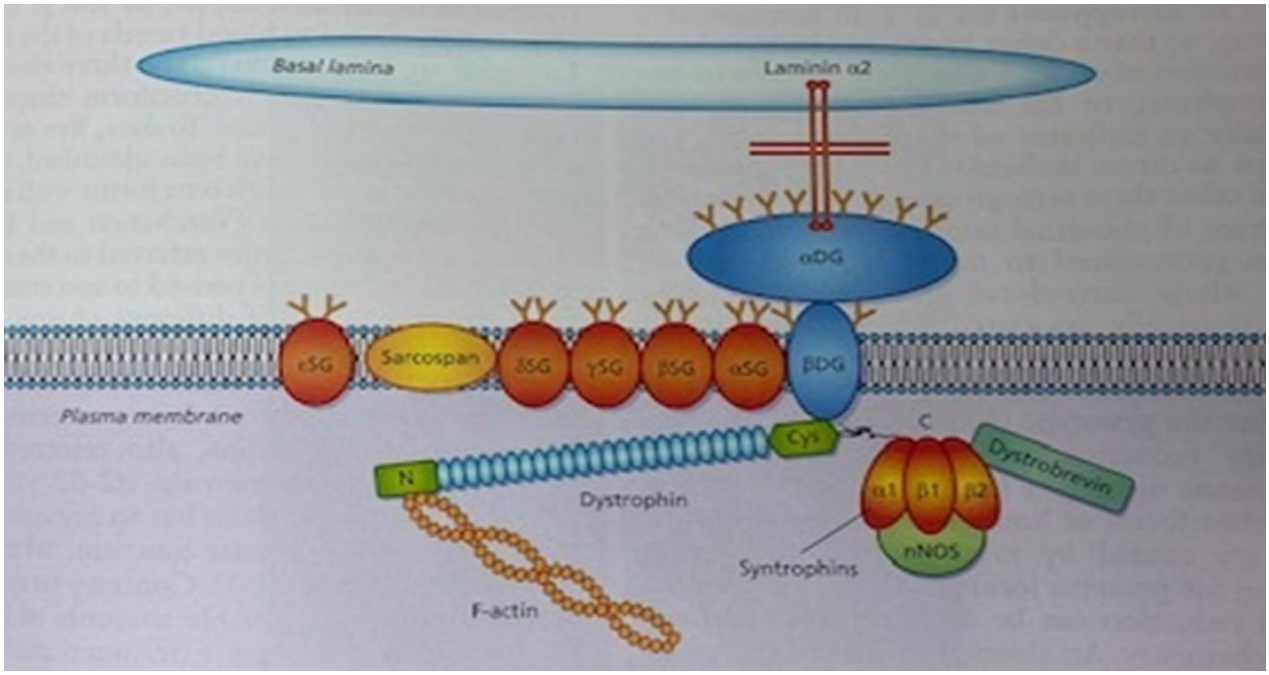
1. Mutations at DMD gene lead to disruption of dystrophin production.
2. The gene for dystrophin is one of the largest known, with 2,5 Mb of DNA and 79 exons. Transcription of the gene is thought to take about 16 hours. The full-length protein has a predicted molecular mass of 427 kDa and has four main domains.
3. The various isoforms of dystrophin are differentially expressed in skeletal, cardiac and smooth muscle, fetal muscle and neural tissue.
4. It has been suggested that the mental retardation that occurs in about 30% of the cases may relate to involvement of the brain isoforms.

Dystrophin is a cytoskeletal protein that lies on the cytoplasmic face of the plasma membrane it interacts with the actin cytoskeleton and a complex of other proteins, the dystrophin- associated proteins. It is believed to act as a link between the extracellular matrix and cytoskeleton, stabilizing the membrane during contraction

Overview of the literature [21]

Clinical features	**Onset at the first 5 years** **Delayed motor milestones** **Progressive proximal weakness** **Contracture of Achilles resulting in tow-walking** **Waddling gait, lumber lordosis** **Difficulty running, hopping, jumping** **Difficulty rising from floor (Gowers' maneuver)** **Difficulty going up stairs** **Calf hypertrophy** **Cramps –BMD rather than DMD**
Ambulation	Lost by 12 years – DMD Ambulant beyond 16 years- BMD
Creatine Kinase	Usually grossly elevated (10-50 times normal) Elevated at birth
Associated features	Cardiomyopathy (invariable in DMD by late teens; variable in BMD) Intellectual impairment (30% of DMD, rare in BMD)
Pathology	Clinical severity cannot be assessed from pathology (necrosis, regeneration, fibrosis, wide variation in fiber size) Split fibers Dystrophin usually absent in DMD Dystrophin usually present but abnormal in BMD, some exceptions to this Reduction of all dystrophin-associated proteins

Table 14.1.

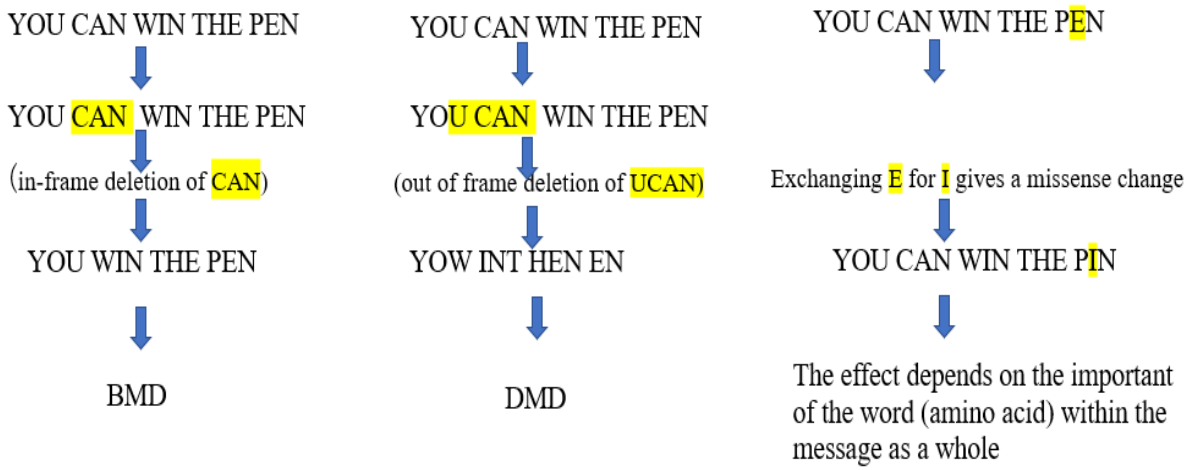


Scheme 14.1.

Distribution of the mutation's types

2/3 mutations are deletions (PCR or MLPA)
1/3 point mutations (WES, IHC)
A very small proportions are duplications (PCR or MLPA).

The possible mechanism for the mutations



Scheme 14.2.

Female carriers of DMD usually show no symptoms of the disease, but may on occasion show minor features such as enlargement of the calf muscle (often unilateral), or muscle cramps; or some may have overt muscle weakness and be as severe as boy with DMD.

The variability in the clinical and subclinical manifestation can be explained by **the Lyon hypothesis** of random inactivation of one X chromosome in every cell, which could be mutated or the normal X chromosome.

There is also evidence, however, of paternal transmission of dystrophin mutations in some carriers

Therapeutic approaches for DMD

1. Gene replacement
2. Reading through of stop codons
3. Exon skipping
4. Others (stimulation of muscle fiber regeneration, stimulation of fiber hypertrophy and limiting fibrosis)

Conclusion

Muscle biopsy plays an important role as part of the diagnostic process in the assessment of a patient with neuromuscular condition. Accurate diagnosis and identification of the pathogenic genetic defect allows to give a proper care to the patients and provide an appropriate genetic counseling for the family for preventing new cases. Also, muscle pathology contributes to the development of target therapies and their application.

This is a relatively simple procedure but implementation and interpretation of the results requests a special training. Historically muscle pathology was a point of interest for pediatric and some adult neurologists who had a spread clinical practice with some rare cases of difficult and life-threatening condition and often it was a family/genetical cases. In order to give a proper care neurologist tries to make a complex assessment of the patient including a small piece of muscle taken from specific most involved part of the body. The complex analysis is possible only if the specialist has a whole information about the patient's condition including clinical, laboratory, imaging and genetical data. General pathologists are not involved in the clinical assessment of the patients and usually not trained for muscle pathology. That is why there is a diagnostical gap in many countries in term of muscle disease.

So, in order to think about the establishment of the diagnostic system we need take into account some peculiarities and existed experience in this field, first of all the preparation of muscle samples needs to keep a follow rules like freeze fixation not a formalin, transportation and actions for prevention of defrosting (special electrical supply system, refrigerator).

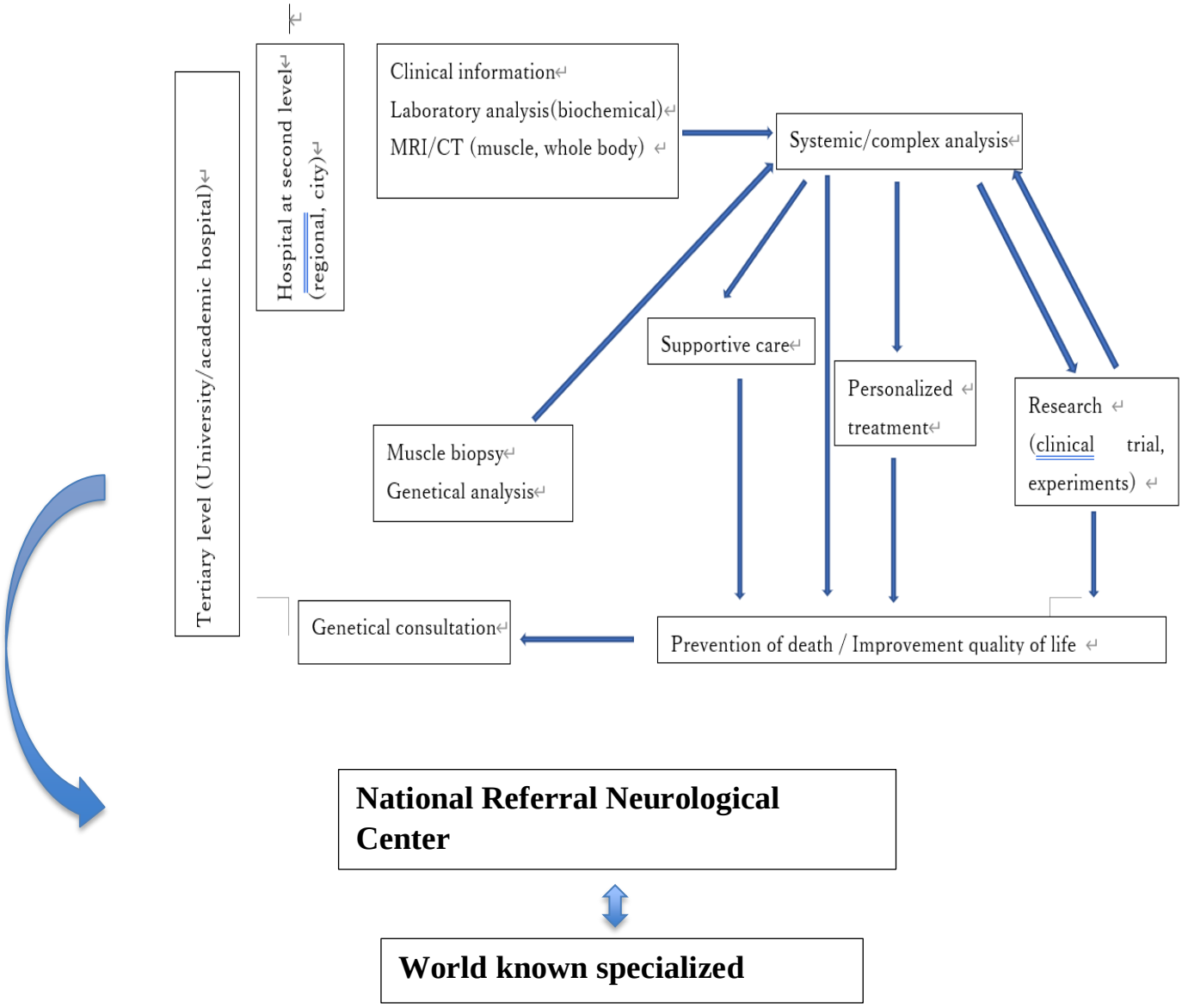
In order to understand the main pathological features of neuromuscular condition we need to be familiar with some key things of neurogenic and myopathic findings.

So, the neurogenic findings on muscle biopsy are follow: a group atrophy and fiber type grouping. These findings will be demonstrating at presentation of neurogenic case. The myopathic findings are follow: necrosis and regeneration, myofibrillar change (e.g., cores), nuclear change, inclusions (e.g., cytoplasmic body, nemaline body), type 1 fiber atrophy and type 1 fiber predominance. All these findings will be described at relevant case presentation.

There are some basic stains which allows to describe majority of cases. The main stains consisting of hematoxilin & eosin, modified Gomori trichrome, reduced nicotineamide adenine dinucleotide-tetrazolium reductase (NADH-TR), succinate dehydrogenase (SDH), cytochrome c oxidase (COX), myosin ATPase and some optional techniques which allows to clarify findings depending on the results after main stains and phenotype (e.g, phosphorylase, alkaline phosphatase, non-specific esterase, acetylcholinesterase and others). Also, in some cases when we expect inflammatory myopathy of some myodystrophies we need to take into account data from immunohistochemistry. Generally speaking, in order to assess

rare neuromuscular disorders, we need to have a specific facilities, technics and well-trained and motivated staff or a diagnostical system.

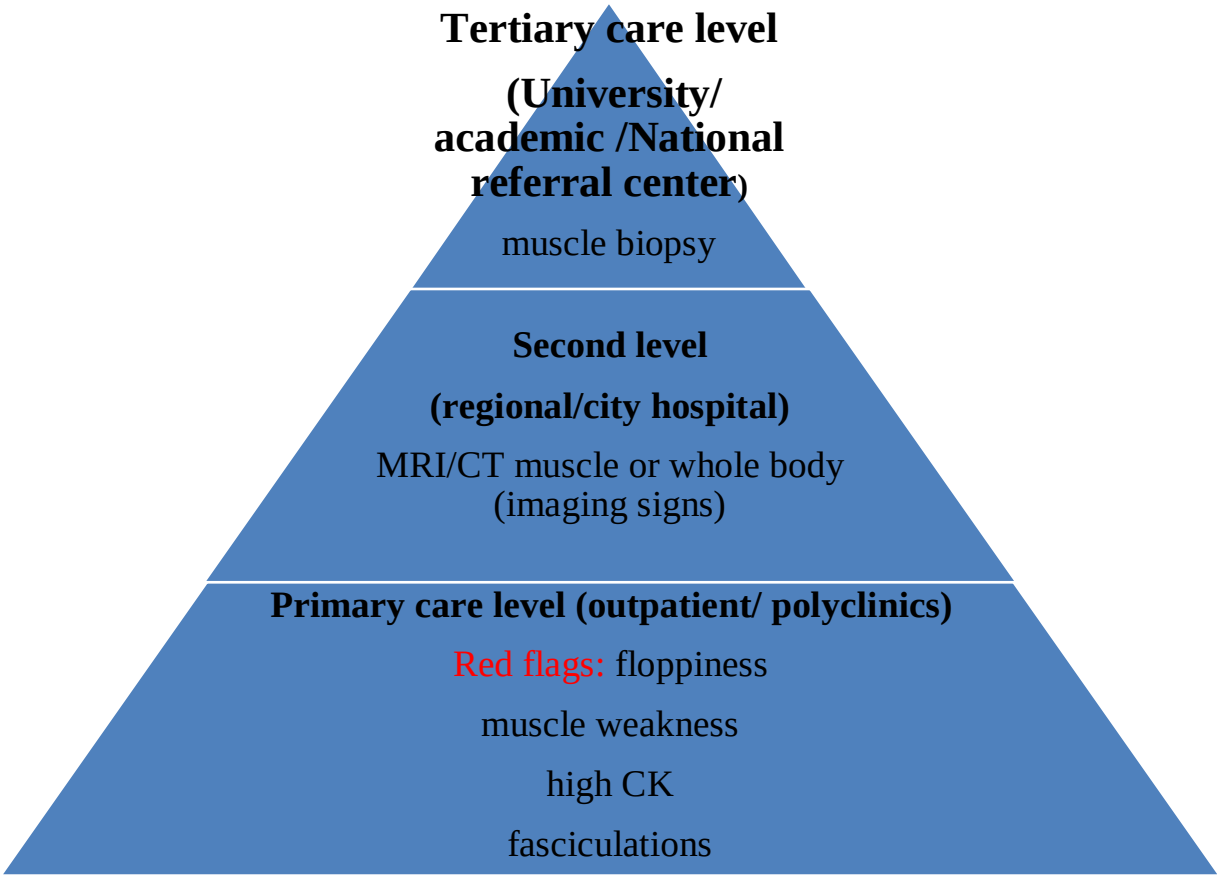
Schematical picture of the management of neuromuscular diseases (and all other rare neurological diseases): Evidence based approach for decision making.



Scheme 14.3.

The diagnostic system should be based on centralization of medical care system and integration of research and clinical facilities. The implementation of such kind of approach is possible on the basis of University or Research institution located in a big central hospital, which is going to work as a country referral center for rare neurological diseases including neuromuscular.

Diagnostical standard of care



Scheme 14.4.

Centralization of all facilities under an umbrella of the National referral center (University/academical hospital) will allow concentration of all resources (human, technical and financial) and developing a highly specialized sustainable diagnostical system for rare neurological/neuromuscular diseases and decrease a burden of these life-threatening condition on health care system.

Appendix 1.

The table with some clinical features that should alert the physicians to consider particular disorders

Clinical features/ Presenting symptom	Disorder/ mutated gene to consider
Hypotonia without muscle weakness	Central or non-neuromuscular problem
Hypotonia with muscle weakness	Congenital myopathies or congenital dystrophies; SMA
Proximal weakness	Common in many myopathies, dystrophies and SMA
Distal weakness	Neuropathies; distal myopathies; myofibrillar myopathies; myotonic dystrophy; inflammatory myopathies (IBM)
Scapuloperoneal/ scapulohumeral weakness	FSHD; laminin A/C Emery-Dreifuss muscular dystrophy; FHL1, MYH7
Asymmetrical weakness	ANO5, FSHD, IBM
Neck weakness including head drop	Congenital myopathies; “dropped head syndrome”, including cases with laminin A/C mutation; myasthenia gravis; endocrine disorders
Early respiratory involvement	Several disorders but consider acid maltase deficiency; SEPN1 core myopathy, SMARD1, HMERF
Axial>limb weakness	Lamin A/C EDMD; core myopathies; some myofibrillar myopathies
Scoliosis	Core myopathies; Ulrich CMD; late-stage dystrophies
Ptosis and /or ophthalmoplegia	DM1; mitochondrial myopathies; myasthenic syndromes; congenital myopathies e.g. centronuclear myopathies, RYR1-related myopathies, TPM2-related myopathies; oculopharyngeal dystrophy; myosin 2a myopathies
Muscle pain/cramps, especially on exercise	Non-specific; BMD some LGMDs; inflammatory myopathies; metabolic myopathies
Fatigue	Myasthenic syndromes; metabolic myopathies e.g. acid maltase deficiency
	Contractures
Elbow	EDMDs
Long finger flexors	Bethlem myopathy

Rigid spine	Lamin A/C; SEPN1 or FHL1
Arthrogryposis	Congenital myopathies, congenital myasthenia
Congenital hip dislocation	RYR1, COL6, SMA2
Distal joint laxity	Non-specific feature but can be a feature of COL6
Associated cardiac involvement	
Arrhythmia/conduction defects	EDMDs; myotonic dystrophy; mitochondrial myopathies
Cardiomyopathy	DMD, BMD; several LGMDs; metabolic myopathies; myofibrillar myopathies; amyloidosis
Central nerve system involvement (considerable overlap but consider some of the following)	
Epilepsy	Metabolic disorders, CMDs
White matter changes on MRI and/or structural changes	
Cataracts	Myotonic dystrophies; αB-crystallin myofibrillar myopathy some congenital myopathies (e.g. DNM2 or TPM3); rare disorders (e.g. Vici syndrome; Marinesco-Sjogren syndrome)
Hearing loss	Mitochondrial myopathies; FSHD
Lipodystrophy	Lamin A/C or PTRF
Rhabdomyolysis	BMD, RYR1, some metabolic disorders
Creatine kinase level	
Normal or mild elevation (2-5x normal)	Congenital myopathies; lamin A/C EDMD; neurogenic disorders; mitochondrial myopathies; inflammatory myopathies
Moderately elevated (5-10x normal)	Many myopathies and dystrophies; inflammatory myopathies
Very high (over 50x normal)	DMD/BMD; dysferlinopathy; calpainopathy; ANO5; sometimes in inflammatory myopathies
Raised serum or CFS lactate	Mitochondrial disorders
Skin changes	
Rash	Dermatomyositis
Follicular hyperkeratosis, keloid formation	Collagen VI disorders
Ichthyosis	CHKB, Chanarin Dorfmann syndrome

Treatable neuromuscular diseases

Gene therapy

5. **SMA**

Oligonucleotides

6. **DMD(ASO)**
7. **SMA(ASO)**
8. **Amiloidosis(RNA)**

Enzyme replacement

9. **Pompe disease**
10. **Fabry disease**

Supplementation

11. **Primary carnitine deficiency**
12. **MADD**
13. **Brown- Vialetto-Van Laere syndrome**
14. **Primary CoQ deficiency**
15. **Thymidine kinase 2 deficiency**
16. **MNGIE**

Immune modulation

17. **Myositis**
18. **Myasthenia gravis**
19.

NMJ transmissionmodulation

20. **Myastnenia gravis**
21. **Lambert-Eaton myasthenic syndrome**
22. **Congenital myasthenic syndrome**

Appendix 3

List of useful websites

National Library of Medicine: PubMED
http://www.ncbi.nlm.nih.gov/pubmed

Online Mendelian Inheritance in Man
http://www.ncbi.nlm.nih.gov/sites/etrez?db=omim

Neuromuscular Disorders, official journal of World Muscle Society (WMS)
http://www.nmd-journal.com

Gene table of Neuromuscular Disorders
http://www.musclegenetable.fr

World Muscle Society
http://www.worldmusclesociety.org

Leiden Muscular Dystrophy pages
http://www.dmd.nl/

Neuromuscular Disease Center,Washington University School of Medicine, St.Louis,MO
http://neuromuscular.wustl.edu/

mutation Database of Inherited Peripheral Neuropathies
http://www.molgen.ua.ac.be/cmtmutations/

The European Neuromuscular Center
http://www.enmc.org

Antibody Resource Pages
http://www.antibodyresource.com/
http://www.glennmorris.org.uk/mabs/WCIND.htm

Developmental Studies Hybridoma Bank
http://dshb.biology.uiowa.edu/

Mitomap. A Human Mitochondrial Genome Database
http://www.mitomap.org/

Questions for test

1. The cause of Pompe`s disease?

+ a. acid maltase deficiency
b. myophosphorylase deficiency
c. phosphofructokinase deficiency
d. deficiency in the branching enzyme
e. dystrophin deficiency

2. A boy, 7 year-old have motor development delayed, and he has difficulty walking. His weakness is predominantly in the proximal muscles. He also has pectoral and shoulder weakness and winging of the scapulas. His calves are enlarged, with a “rubbery” texture. His intelligence quotient (IQ) is low. His serum creatine kinase is 13,240 IU/L . A muscle biopsy is obtained, which is shown in Figure 1. Which of the following is the most likely diagnosis?

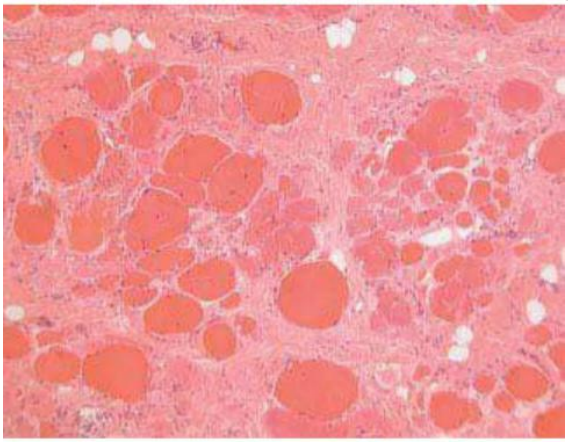


Fig 1.

a. Becker muscular dystrophy
+b. Duchenne muscular dystrophy
c. Fascioscapulohumeral muscular dystrophy
d. Limb-girdle muscular dystrophy
e. Spinal muscular atrophy

3. X-linked recessive disorder in which there is progressive atrophy or degenerative changes in muscle fibers, with the primary abnormality in an intracellular protein, dystrophin
+a) Duchenne's muscular dystrophy
b) myotonic dystrophy
c) polymyositis
d) rhabdomyelitis
e) congenital myotonia

4. What is the pathophysiology of patients with Spinal Muscular Atrophy (SMA)?
a. Neuromuscular junction blockage
b. Muscle denervation at the peripheral nerves
c. Posterior horn cell loss
+d. Anterior horn cell and interneuron loss

e. Necrotic and regeneration process in muscles

5.Serum creatine phosphokinase activity level in spinal muscular atrophy:
a. increases significantly
b. slightly elevated
c. not analyzed
d. rises
+e. within normal range

6. A characteristic electromyographic sign of damage to the motor neuron of the spinal cord in spinal atrophy is
+a. picket fence rhythm
b. myopathic lesion rhythm
c.reduction of impulse conduction speed less than 38 m/s
d. does not change
e. positive decrement test

7.Specify the localization of lesions in hereditary progressive muscular dystrophy?
a. Damage to the cerebral cortex
b. Damage to the peripheral nervous system
c. lesions of the anterior horns of the spinal cord
d. Lesion of the lateral cord of the spinal cord
+e. muscle pathology

8. Which of the following forms of progressive muscular dystrophy are primary?
a. Charcot-Marie-Tooth neural amyotrophy
+b. Duchenne myodystrophy
c. Immune mediated necrotizing myopathy
d. Spinal muscular atrophy 5q
e. Myasthenia gravis

9. Select the subtype of SMA, which is characterized by the following criteria according to the system of the International SMA Consortium: age of onset 6-18 months, maximum motor functions - sitting independently, some stand at the support, do not walk, can live up to 25 years:
a. SMA type 1
+b. SMA type 2
c. SMA type 3
d. SMA type 4
e. SMARD

10. Dosing regimen for nusinersen?

+a. 4 doses of initiation of therapy: 12 mg / 5 ml intrathecally 0-14-28-63 days, then 1 time / 4 months.
b. once intravenously at the rate of 1.1*10 14 vg/kg
c. daily inside at the rate of: up to 2 years 0.2 mg / kg, from 2 years with a weight of less than 20 kg, 0.25 mg / kg, from 2 years with a weight of more than 20 kg, 5 mg
d. 1 ml intramuscularly 1 time/year
e. per os, daily

11. The main cause of spinal muscular atrophy 5 q is?
a. hemizygous mutation in the RMD gene;
b. a heterozygous mutation in the TTN gene;
+c. homozygous deletion of exons 7-8 of the SMN1 gene
d. homozygous mutation in the FKTN gene
e. mutation in ASAH gene

12. Distal forms of spinal muscular atrophy are predominantly inherited as:
a. X-linked recessively;
b. X-linked- dominant;
+c. autosomal dominant
d. autosomal recessive
e. occasional point mutation

13. The initial signs of Erb myopathy include:
a. Cervical muscle weakness
b. Weakness of distal arm muscles
+c. Muscle weakness in the proximal arms and shoulder girdle
d. Weakness of distal legs
e. Rigid spine

14. How does gait change in myopathy in children?
a. Spastic gait
b. Atactic gait
+c. Waddling gait
d. "Steppage"
e. The gait is pretentious, unusual

15. The presence of myodystrophy in the clinical picture of the disease is typical for
a. structural myopathies
b. spinal atrophy

c. hereditary neuropathies
+d. progressive muscular dystrophies
e. myasthenia

16. For Progressive muscular dystrophy Emery - Dreyfus is not typical:
a. localization of muscle atrophies mainly in the triceps and biceps muscles, muscles of the pelvic girdle, thighs and peroneal group
b. atrophy of the muscles of the face, shoulder girdle and anterior leg muscles
c. slowly progressive course
d. the presence of flexion contractures in the elbow joints, retraction of the calcaneal tendons, stiffness in the cervical spine
+e. muscle pain

17. Spinal muscular atrophy type 3 has an onset at the age of:
a. 6-18 months
b. up to 6 months.
+c. >18 months
d.30-40 years old.
e. at birth

18. X-linked myodystrophy does not include:
a. Becker's muscular dystrophy
+b. Erb's myodystrophy
c.Duchenne myodystrophy
d. Leiden-Moebius myodystrophy
e. Emery-Dreyfus myodystrophy

19. In which enzymes increase in the blood is characteristic of Duchenne myodystrophy?
a. amylase
b. LDG
+c. CK
d. acid maltase deficiency
e. ALT, AST

20. What functional scale is used to assessment of motor skills for non-ambulant SMA patients?
+a. CHOP-INTEND
b. RULM
c. 6-MWT
d. Brooke scale

f. MFM

21. What antibody is present in myasthenia gravis?
a.HLA-B27
b.Anti-ds DNA
+c. Anti-AChR
d.Anti-Smith
e. HLA-DR

22. What symptom is not expected in patients with myasthenia gravis?
a. muscle weakness
+b. Impairment of memory
c. ptosis
d. difficulty in speech
e. respiratory failure

23. Neuromuscular disorders can be associated with:
    a Autonomic dysfunction.
    b Fibrotic lung disease.
    c Obstructive sleep apnoea.
    +d Heart block.
    e Gastric stasis.
24. Complications of neuromuscular disorders include:
    a Hyperkalaemia.
    b. Hypothermia.
    +c. Muscle rigidity.
    d. Alkalosis.
    e. Reduced creatine kinase (CK) concentration.
25. Myotonic reactions:
    a. Are always associated with malignant hyperthermia.
    b. Are due to reduced sodium influx.
    c. Can be triggered by succinylcholine.
    +d. are due to reduced chloride conductance
    e Can be triggered by opioids.
26. Treatment of myotonic reactions can include:
    +(a) Treating the precipitant.
    (b) Dantrolene.
    (c) Class III anti-arrhythmic agents.
    (d) Alkalinization of urine.
    (e) Analgesia.
27. Regarding Duchenne muscular dystrophy:
    +a It is the most common childhood neuromuscular disorder.
    b It is an autosomal dominant condition.

c Cardiomyopathy is common.

d Distal muscles are affected by wasting and weakness.

e. Depolarizing muscle relaxants can be used safely.

28. Regarding myotonia congenital:

a. It is an X-linked disease.

+b. Symptoms result as the consequence of an abnormal sodium channel.

c. Widespread muscle hypertrophy occurs.

d. Topical administration of local anaesthetic may aid relaxation of muscle contractures.

e. It is a pre-junctional disorder.

29. Neuromuscular junction disorders:

+a all mentioned answers

b. Can be worsened by antibiotic administration.

c. Can be associated with malignancy.

d. Can show sensitivity to non-depolarizing muscle relaxants.

e. May be treated with cholinesterase inhibitors.

30. Which of the following agents is NOT known to exacerbate neuromuscular weakness?

a.methylprednisone

b. rocuronium

c. aminogylcosides

+d. cephalosporins

e. non above

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