5th Congress of the European Academy of Neurology

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Teaching Course 10

Clinical science in muscle disorders (Level 2)

Diaphragmatic weakness

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Clinical science in muscle disorders

Diaphragmatic weakness

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Hôpitaux Universitaires Paris Ile-de-France Ouest
RAYMOND POINCARÉ • BERCK
AMBROISE PARÉ • SAINTE PÉRINE

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UNIVERSITÉ DE VERSAILLES ST-QUENTIN-EN-YVELINES

Disclosures

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Diagnosis and management of neuromuscular disorders: basic principles

- Assessment of limbs and axial muscle weakness
- Systematic cardiac examination : ECG + echocardiography
- Systematic evaluation of respiratory function : PFT +/- blood gas

→ *These parameters are crucial for diagnosis and the follow-up of the patients*

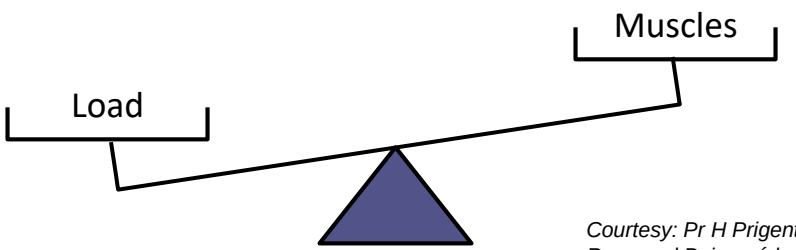
Respiratory insufficiency in neuromuscular disorders

- Usually occurs in adults with advanced stages of the disease:
  - Duchenne, SMA, Limb-girdle muscular dystrophies (sarcoglycanopathies, FKRP…)
- But also occasionally at disease onset, or as a predominant symptom:
  - Some muscle disorders may reveal through acute respiratory failure, and thus referred by pneumologists or intensive care units doctors

Neuromuscular respiratory failure

- Paralysis of respiratory muscles
  =>Failure of the respiratory pump

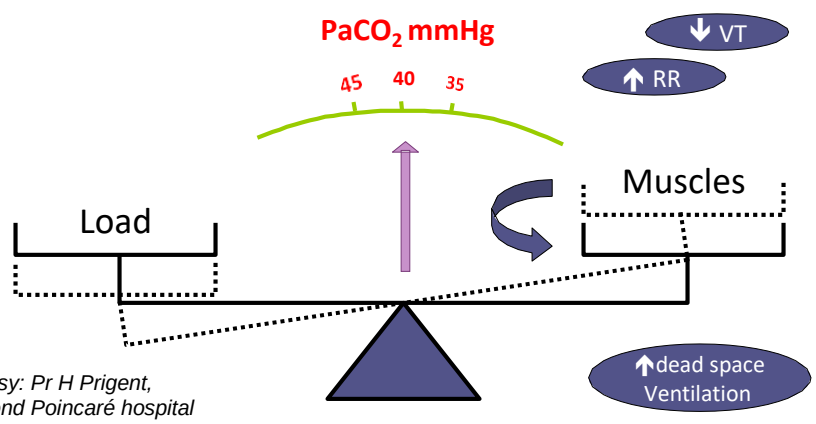
Nava 1996, Misuri 2000, De Troyer 1980
Vitacca 1997, Brack 2002, Estenne 1993



Courtesy: Pr H Prigent,
Raymond Poincaré hospital

Neuromuscular respiratory failure

=> Adaptative mechanisms



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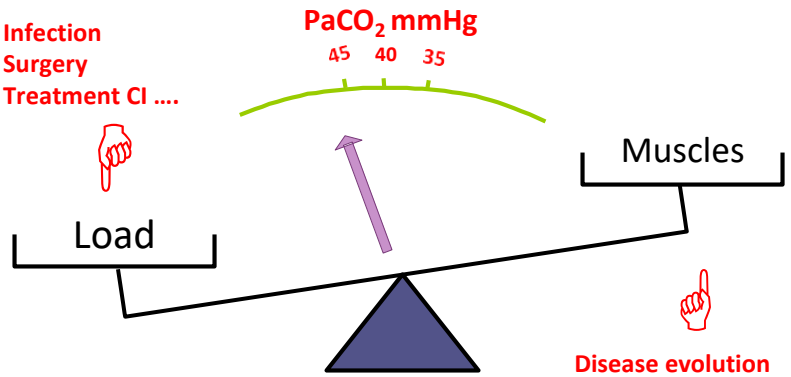
Neuromuscular respiratory failure

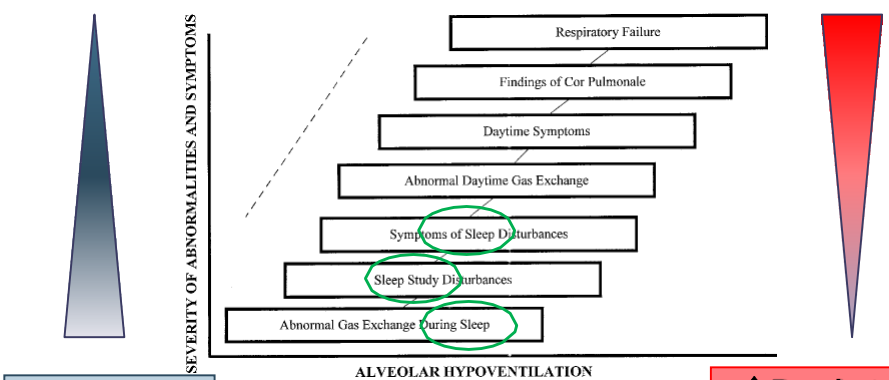


⇒Hypercapnic respiratory failure

⇒Early impairment of nocturnal ventilation

Courtesy: Pr H Prigent, Raymond Poincaré hospital

Neuromuscular respiratory failure



↓ Vital Capacity

Chest2002,

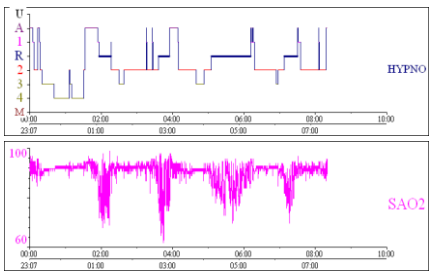
↑ Respiratory handicap

Neuromuscular respiratory failure

Early impairment of ventilation **during night time**

Ragette, 2002; Hukins, 2000; Arnulf, 2000
Ferguson, 1996; Khan, 1994

Apnea/Hypopnea



Courtesy: Pr H Prigent, Raymond Poincaré hospital

Neuromuscular respiratory failure

- **Expiratory muscles involvement =**
  - ↓ cough efficiency

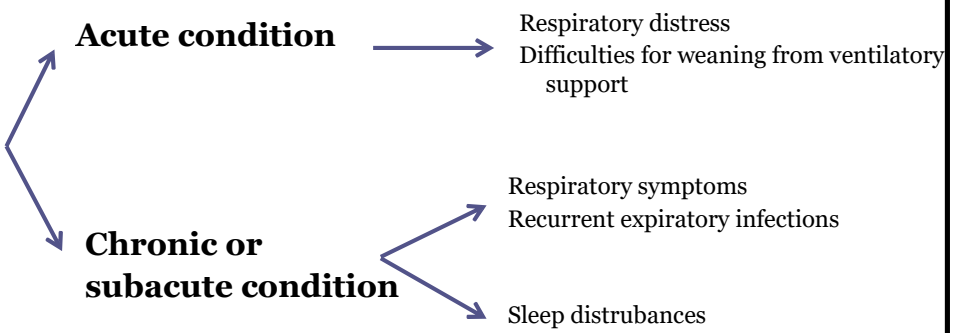
- **Upper airway muscles involvement**

Bulbar involvement or muscular failure:

  - ↓ cough efficiency
  - ↓ lower airways protection
  - ↑ obstruction during sleep

Courtesy: Pr H Prigent, Raymond Poincaré hospital

NMD with inaugural respiratory insufficiency



Courtesy: Pr H Prigent, Raymond Poincaré hospital

Respiratory insufficiency in NMD: Insidious onset and few complaints from patients

- Dyspnea generally moderate
- Orthopnea
- Dyspnea when leaning forward
- Paradoxical respiration
- Superficial polypnea

- Daytime sleepiness
- Headaches
- Sleep disorders
- Cognitive impairment and mental confusion

Respiratory insufficiency in NMD: Insidious onset and few complaints from patients

- Dyspnea generally moderate
- Orthopnea

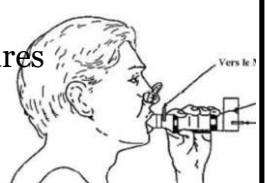
Symptoms of respiratory failure are very late

= Danger +++

- Sleep disorders
- Cognitive impairment and mental confusion

Functional evaluation

- PFT: Assessment of vital capacity in sitting and supine positions: diaphragmatic dysfunction if difference > 20 %
- Non invasive assessment of respiratory pressures
  - ↓ of MIP and/or SNIP
  - ↓ of MEP



- Blood Gas: alveolar hypoventilation => Hypercapnia (late)
- Respiratory polygraphy or polysomnography:
  - Hypoventilation ++
  - Hypopnea/central apnea and/or obstructive,
  - mixed syndromes

Courtesy: Pr H Prigent, Raymond Poincaré hospital

Clinical cases of myopathies revealed by severe diaphragmatic weakness

Case N°1

- 38-year-old man consulting his GP for lower limbs oedema
- Medical history: smoking 15 pack-years
- No family history of NMD
- Referred to emergency unit for suspicion of pulmonary embolism
- Other symptoms: tachycardia and dyspnea
- General and vital signs:
  - Poids (kg) : 85 Taille (m) : 1,60 BMI : 33
  - Temp ° C : 37.3
  - TA (mmHg) : PAS= 111 PAM= 84 HR (bpm) : 75
  - RF (c/mn) : 22 SaO2 (%) : 94 with 3L O2, 80 % with O2

Ancillary exams

- Chest X-ray
  - No infection
  - Cardio-thoracic index = 0,57
  - Bronchial syndrome
- Vessels CT-scan: absence of pulmonary embolism
- echocardiography : absence of shunt, normal LVF

Evolution

Non invasive ventilation with full-face mask, then nasal Bipap

Improvement of respiratory symptoms and blood gases

- Blood gas with NIV :
  - pH: 7.53
  - PCO2: 4.17 kPa (ant: 8.34)
  - HCO3- :26.1
  - PO2: 20.6 kPa (ant: 13.6)
  - Sat: 99.5 %
- VC: 54% (2.2L) MIP: 22, MEP:33 cm H2O

Other symptoms

- Diffuse but moderate muscle weakness: 4/5 MRC ⟶ patient referred to neurologist
- Hand myotonia *
- Facial weakness and bilateral ptosis *
- Dysarthria *
- Baldness *
- * these symptoms were not detected by the GP and pneumologist, and the patient was not complaining

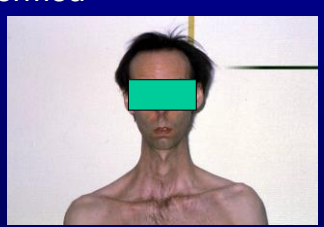
Other symptoms

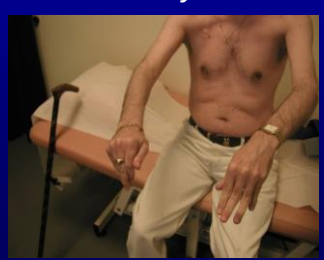
- Diffuse but moderate muscle weakness: 4/5
-
-
-
-
- * these symptoms were not detected by the GP and pneumologist, and the patient was not complaining about

Diagnosis:
Myotonic dystrophy type 1 /Steinert disease
Most frequent myopathy in adults

Respiratory insufficiency in DM1/Steinert disease

- Very frequent manifestation of the disease even in patients able to ambulate unaided
- Inaugural complication in some cases
- Major cause of morbidity/mortality in DM1
- Patients most often don't complain of symptoms
- PFT + blood gas measurement should be systematically performed





Case N°2

Case n°2

- 43-year-old woman
- Hospitalized in ICU for acute respiratory distress
- Background :
  - Returned from a trip in Asia
  - Left basal pneumonia since 2 days with hypoxia

Clinical examination

- PA : 154/92; HR : 127; SaO2 : 100% with 15 L O2; FR : 30/min
- Sleepy patient
- Pulmonary exam :
  - Paradoxical abdominal respiration
  - Low thoracic movements
  - Ineffective cough
  - Use of accessory respiratory muscles
- Blood gas : pH 7,11 ; PCO2 122 mmHg ; PO2 86 mmHg, HCO3- 39 mmol/L, lactate 0,47 mmol/L

Emergency care

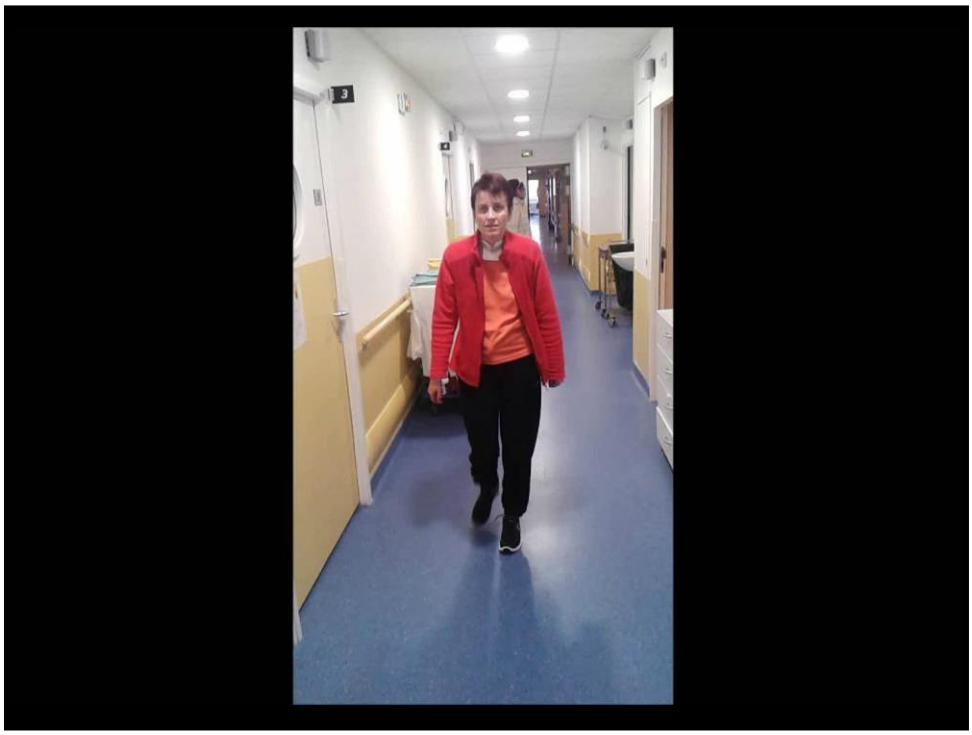
- Transfer to hospital intensive care unit
- Intubation and mechanical ventilation
- Bronchial fibroscopy and aspiration

Neurological examination

- Proximal lower limbs muscle weakness :
  - Muscle testing: 4/5 on MRC scale
- Absence of atrophy
- No fasciculation
- Presence of DTR, and absence of pyramidal syndrome
- No sensory deficit
- No ophtalmoplegia

Detailed patient interview

- Delayed motor milestones:
  - walked at age of 2 years
- Difficulties for sport activities at school :
  - always exempted
- Progressive lower limbs weakness since 2 years with difficulties for climbing stairs and raising from a chair :
  - professional redeployment !



Ancillary exams

- CPK: 300 UI/L
- ENMG:
  - Myopathic pattern
  - Pseudo-myotonic discharges
- ECG: normal, absence of conduction or rhythm anomaly
- Echocardiography :
  - Absence of dilated or hypertrophy cardiomyopathy
  - Normal LV ejection fraction
- Acid alpha-glucosidase deficiency in leucocytes

Late-onset Pompe disease or acid maltase deficiency (LOPD)

- First descriptions by Hudgson P. *et al.* (Brain, 1968) and Engel AG. (Brain, 1970)
- Pelvic girdle weakness which may mimic muscular dystrophy or other myopathies
- Respiratory insufficiency due to diaphragmatic paralysis during the course of the disease
- Inaugural respiratory failure as first symptoms of the disease in some patients (Lightman NI and Schooley RT, Chest, 1977; Trend PS *et al*., Brain, 1985)
- Possibility of prolonged survival with respiratory assistance

Late-onset Pompe disease: frequent diaphragmatic involvement at various ages

Absence of correlation between severity of limb muscle weakness and diaphragmatic involvement

Case n°2 : follow-up

- Weaning from tracheostomia after a few months
- Severe diaphragmatic weakness assessed by by PFT :
  - CV = 1270 ml (34 %)
  - MIP = 12 cm H2O, MEP = 30 cm H2O
- Nocturnal ventilation
- Enzyme replacement therapy since 2015 (Myozyme ®) : 20 mg/kg infusion every other week
- Stabilization of diaphragmatic weakness and walking difficulties

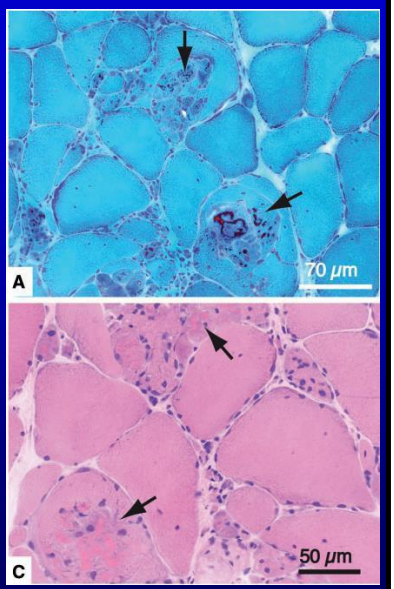
Case N°3

Case n°3

- 27-year-old man of Portuguese origin
- Family history: parents are first cousins
- Regular sports activities: swimming and fitness
- 26 years: occurrence of dyspnea and muscle fatigability during exercise leading to interruption of sport activities
- 27 years: coma and cardio-pulmonary arrest during skiing
- Intubation and mechanical ventilation:
  - Right basal pneumonia
  - Acute respiratory distress

- Transfer to Garches hospital
- Severe diaphramatic weakness assessed by diaphragmatic ENMG
- PFT:
  - Sitting VC : 1960 ml 35 % /Supine VC : 1270 ml 22 %
  - MIP = 37 cm H2O, MEP = 135 cm H2O
- Clinical examination:
  - Left peroneal nerve palsy
  - Mild weakness of ilio-psoas
  - No ophtalmoplegia or swallowing difficulties
- Normal CK levels
- Normal acid alpha-glucosidase activity

- ENMG
  - Sensory-motor axonal neuropathy asymmetric with denervation
- Neuromuscular biopsy:
  - Nerve:
    - Major axonal involvement
    - Absence of amylosis
  - Muscle:
    - Atrophy with denervation
    - Agregates on Gomori Trichrome



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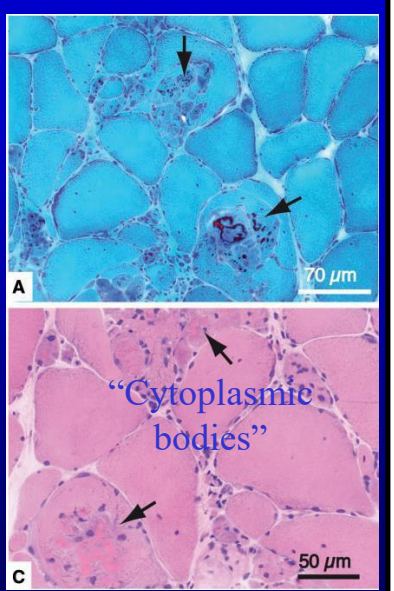

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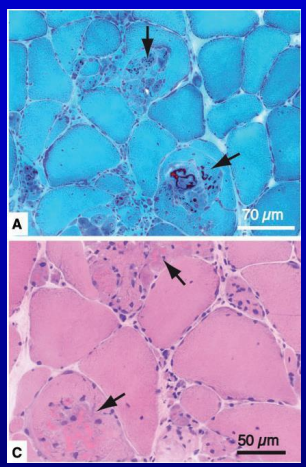
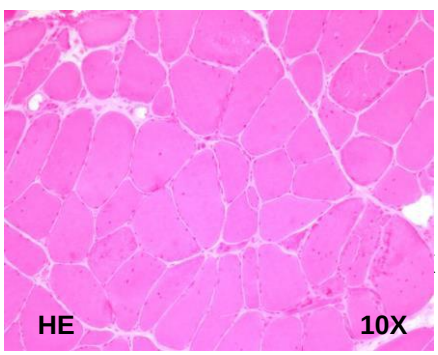
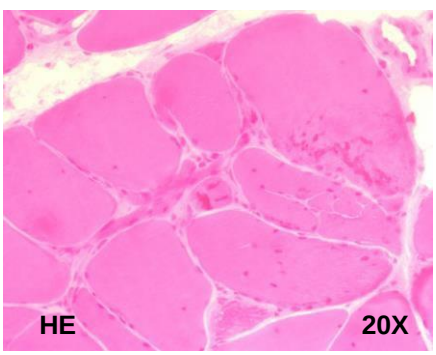


Further analysis on a deltoid muscle biopsy

(Edoardo Malfatti and Norma B. Romero)

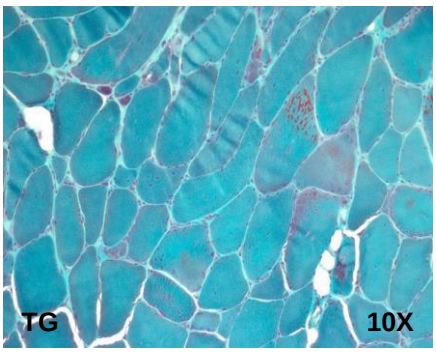


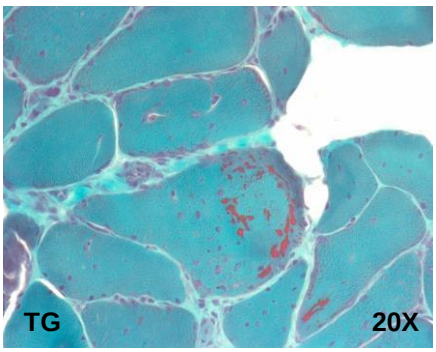


Frozen sections

Unité de Morphologie Neuromusculaire – Institut de myologie – Pavillon Risler
Groupe Pitié –Salpêtrière – 47 Bld de l'Hôpital – 75651 Paris Cedex13
☎ 01 42 16 22 42 – 22 43 🖷 01 42 16 22 40

Biopsy 12/11/1999 ref. GE 458475: Left Deltoid





Frozen sections

63X

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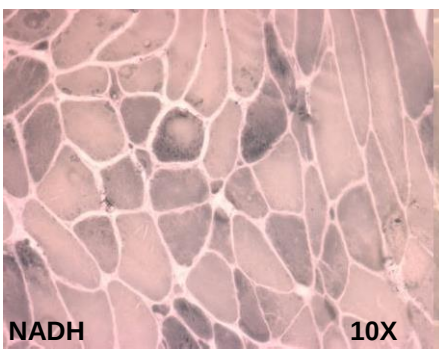

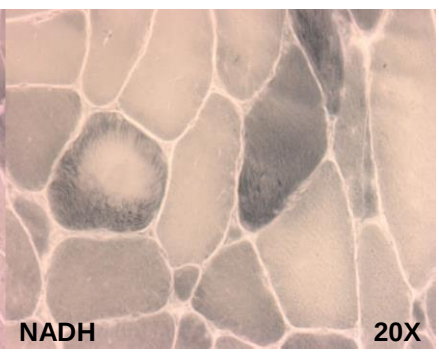

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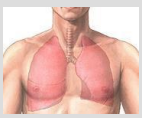
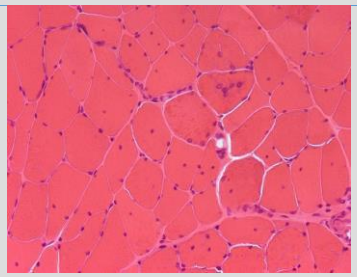
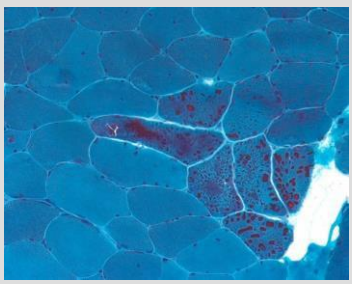
HMERF: hereditary myopathy with early respiratory failure (Titin gene)

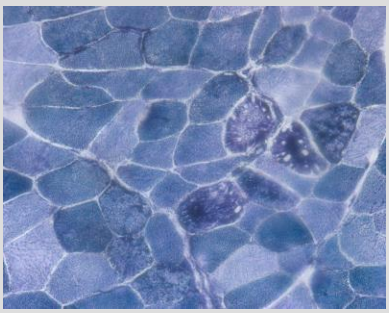


exon 343

TTN: NM_001267550.1







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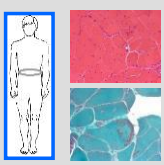

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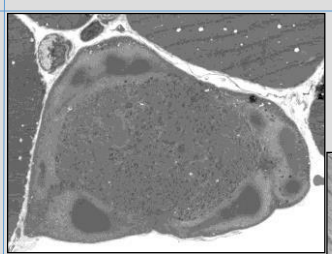
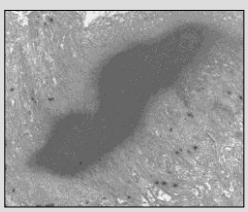
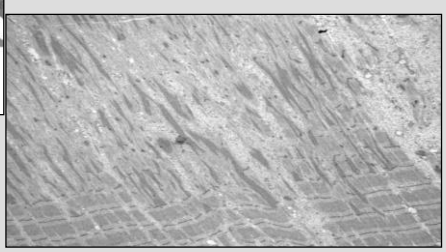
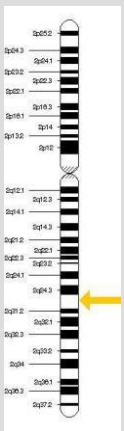




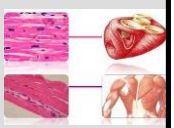


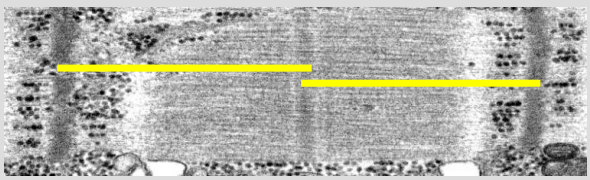
TTN

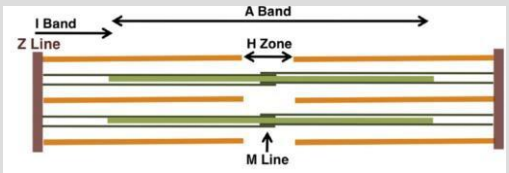
2q31



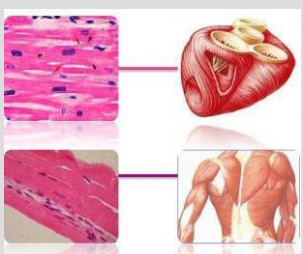
Titin







Titin-related myopathies



- CARDIOMYOPATHIES
  - DILATED
  - HYPERTHROPHIC
- SKELETAL MUSCLE MYOPATHIES
  - TMD
  - LGMD2J
  - HMERF
  - EARLY-ONSET MYOPATHIES ± CONTRACTURES OR CARDIOMYOPATHY

Take-home messages (1)

- Systematically evaluate respiratory function in case of suspicion of NMD, and collaborate with dedicated physiologist and pneumologists
- Ideally always perform PFT with:
  - sitting and supine VC assessment
  - MIP, MEP and SNIP
  - +/- polysomnography
- Respiratory muscle involvement may occur in most NMD at various stages of the disease course according to the etiology
- Ventilation may help to prolong life for years and decades…

Take-home messages (2)

- Respiratory insufficiency may be predominant in specific disorders, showing the importance of establishing a correct diagnosis
- Main “myopathic” causes (Naddaf E and Milone M, Muscle and Nerve, 2017):
  - Pompe diseas
  - Myotonic dystrophy type 1
  - Myofibrillar myopathies: Desmine, Filamin C, *FHL1*
  - Cytoplasmic body myopathy: Titin
  - Multi-minicore disease (*SEPN1*), *MEGF10* related myopathies
  - MELAS, Laminopathy, Centronuclear myopathy

Take-home messages (3)

- Action to be taken in a patient with "isolated" diaphragmatic impairment ::
  - Assess the neurogenic or myopathic origin if possible: clinical history and examination, ENMG of limbs and diaphragm (?)
  - Perform blood analysis for CK, lactate, acid alpha-glucosidase, anti-Rach and anti-Musk Ab
  - Discuss the muscle biopsy even in the absence of muscle weakness and in case of normality of all ancillary exams

Acknowledgments

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- Pr David Orlikowski (Intensive care unit, Garches hospital)
- Dr Edoardo Malfatti (Neurology department Garches hospital)
- Pr Bruno Eymard (Myology Institute, Pitié-Salpêtrière hospital)
- Dr Norma Romero (Myology Institute, Pitié-Salpêtrière)