Muscle disease in cystinosis

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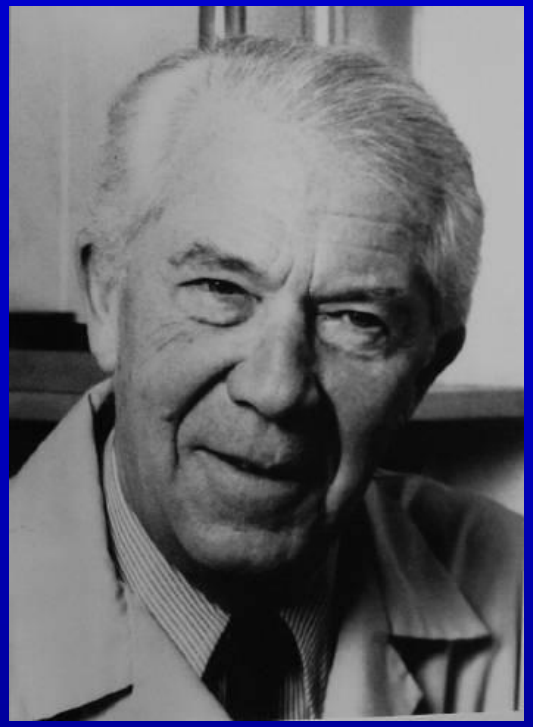
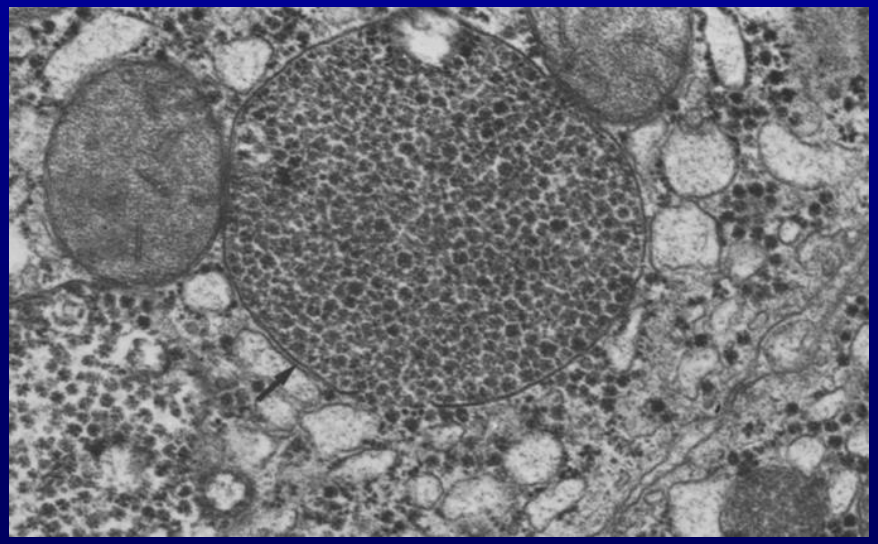
Lysosome discovery

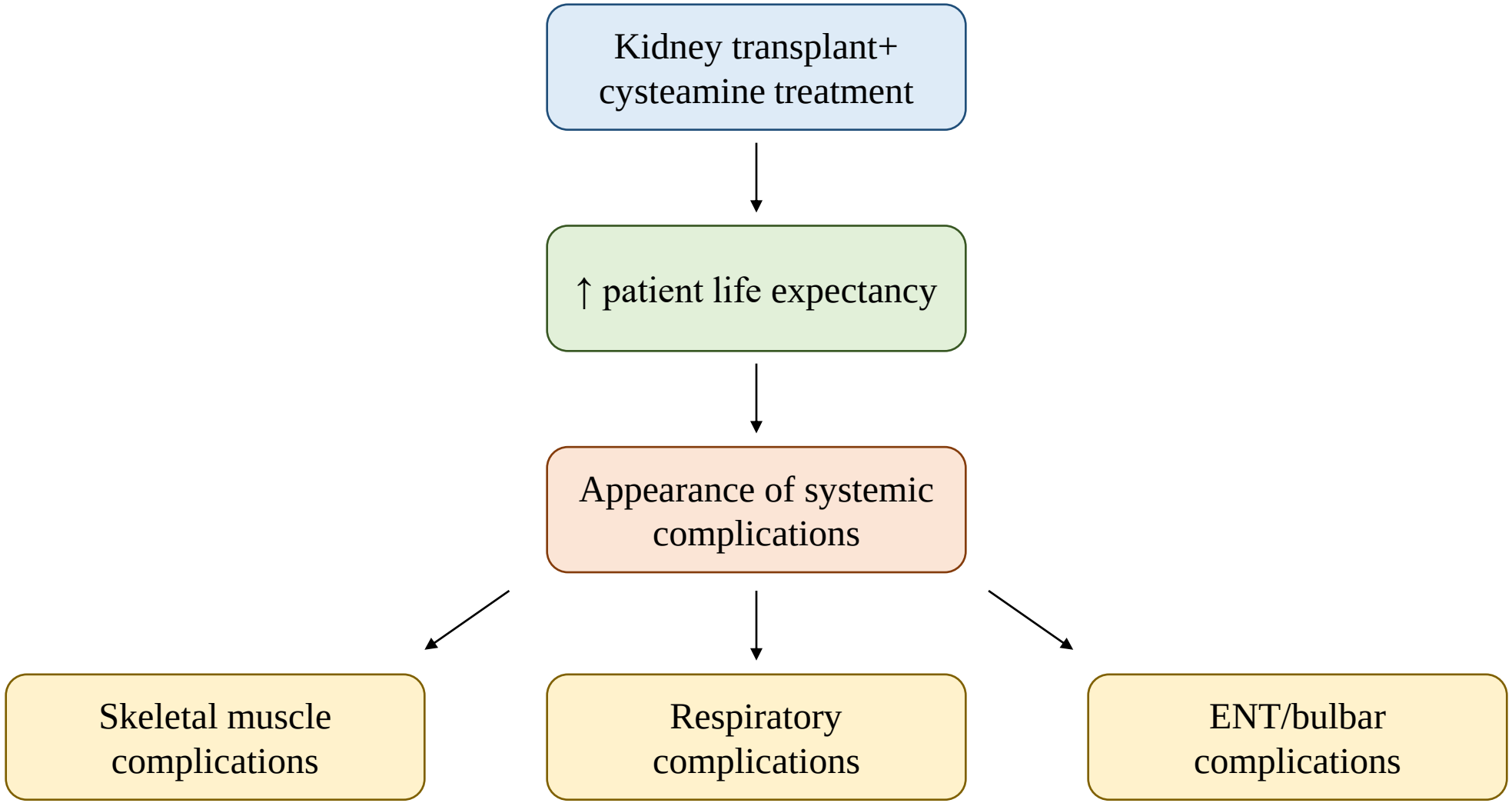


- Christian de Duve (1917-2013)
  - Prix Nobel de médecine 1974 (avec Albert Claude et George Palade)
  - Identification des lysosomes par fractionnement subcellulaire et ultracentrifucation différentielle (1955)
  - Distribution de la phosphatase acide dans les fractions contenant les lysosomes
  - Description de l'autophagie en 1963



- Alex Benjamin Novikoff (1913-1987)
  - Découverte du lysosome en microscopie électronique (1956)

Neuromuscular manifestations of cystinosis



Skeletal muscle manifestations in cystinosis

Myopathy and Cystine Storage in Muscles in a Patient with Nephropathic Cystinosis

New England Journal of Medicine, 1988

William A. Gahl, M.D., Ph.D., Marinos C. Dalakas, M.D., Lawrence Charnas, M.D., Karl T.K. Chen, M.D., Gholam H. Pezeshkpour, M.D., Toichiro Kuwabara, M.D., Suzanne L. Davis, M.B., Ch.B., Russell W. Chesney, M.D., John Fink, M.D., and H. Terry Hutchison, M.D.

Skeletal muscle damage :

- First described in 1988
- Little knowledge on the subject
- Appearance ≈ 20-30 years
- ≈ 24% of cystinosis renal transplant patients

Distal vacuolar myopathy

→ **progressive distal muscle wasting and weakness**

Clinical symptoms :

- ➢ Impairment of the intrinsic muscles of the hand
- ➢ Weakness of upper and/or lower distal limbs
- ➢ Muscle atrophy and/or contracture

Distal Vacuolar Myopathy in Nephropathic Cystinosis

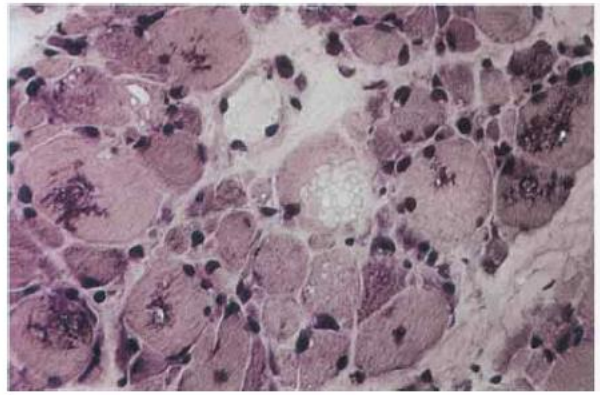
Lawrence R. Charnas, MD, PhD,* Carlos A. Luciano, MD,‡ Marinos Dalakas, MD,§ Roger W. Gilliatt, MD,‡†
Isa Bernardini, MEd,* Kamal Ishak, MD, PhD,‖ Valerie A. Cwik, MD,¶ Douglas Fraker, MD,#
Thomas A. Brushart, MD,** and William A. Gahl, MD, PhD*

Annals of Neurology, 1994

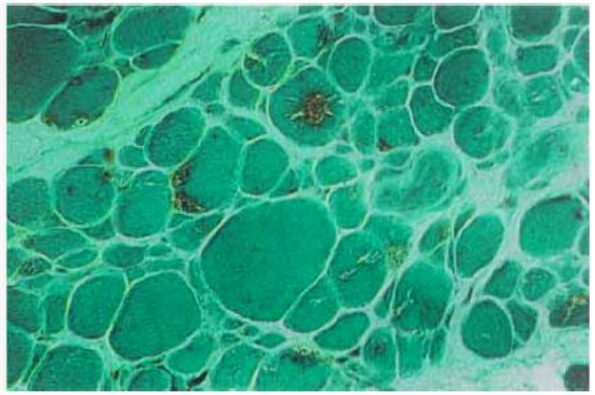
- 13/54 post-renal-transplant patients developed weakness and wasting in the small hand muscles, with or without facial weakness and dysphagia. Tendon reflexes were preserved and sensory examinations were normal.
- Electrophysiologic studies in 11 affected patients showed normal nerve conduction velocities and preserved sensory action potentials.
- Biopsy of the severely affected abductor digiti minimi or extensor carpi radialis brevis muscles in 2 patients revealed marked fiber size variability, prominent acid phosphatase-positive vacuoles.
- Crystals of cystine were detected in perimysial cells but not within the muscle cell vacuoles. The muscle cystine content of clinically affected muscles was markedly elevated.
- Conclusion :distal vacuolar myopathy is a common late complication of untreated nephropathic cystinosis.

Muscle biopsy analysis of cystinosis myopathy

(LR Charnas et al. Ann Neurol, 1994)



A



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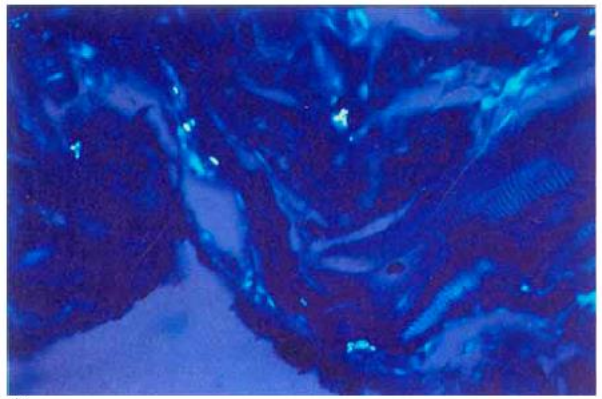
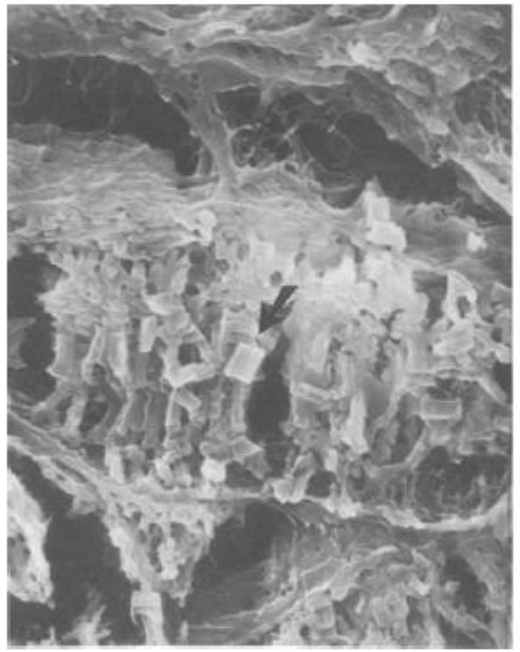


C

Fig 3. Light microscopy of abductor digiti minimi muscle of Patient 1. (A) Marked fiber size variation, increased connective tissue, and prominent rimmed and unrimmed vacuoles are apparent. Hematoxylin and eosin stain (× 475 before 30% reduction). (B) Acid phosphatase–positive staining of the vacuoles reflects their lysosomal origin (× 475 before 40% reduction). (C) Cystine crystals under partially cross-polarizing light (× 450 before 31% reduction). Note striations in muscle fibers.



B

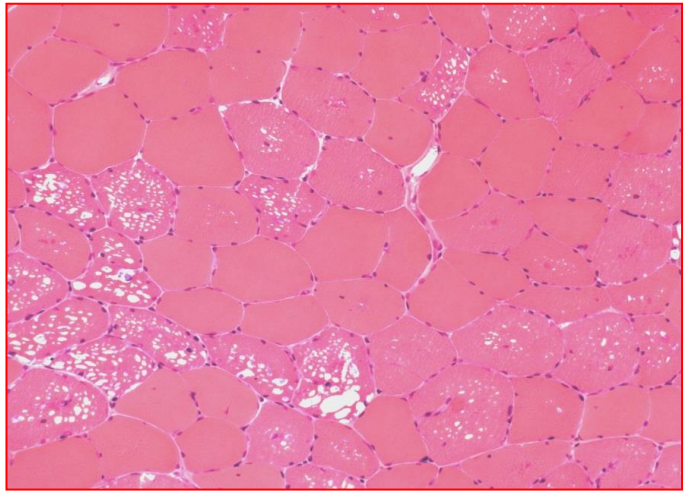
Fig 4. Electron microscopy of cystine crystals. (A) Transmission electron micrograph shows rectangular cystine crystals in the perimysial collagen (× 20,916 before 29% reduction). (B) Scanning electron microscopy shows the three-dimensional appearance of the crystals (× 4,000 before 9% reduction).

Muscle pathology in other lysosomal muscle disorders

Pompe disease

(acid glucosidase deficiency)

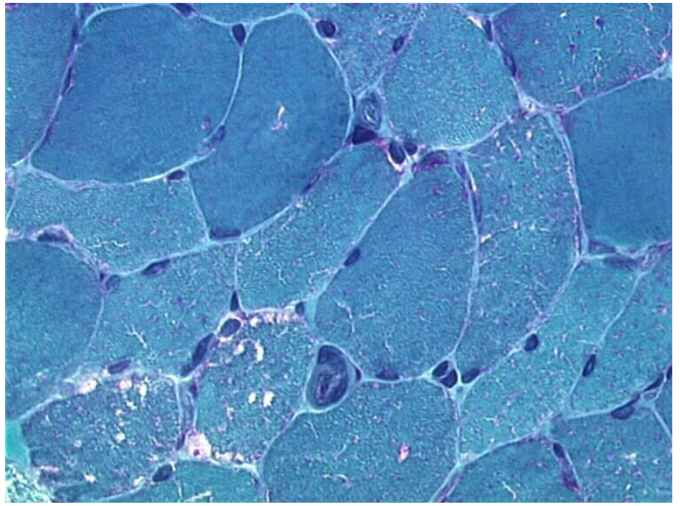
- Children and adult forms
- Cardiomyopathy (children)
- Proximal muscle weakness
- Respiratory insufficiency



Danon disease

(LAMP-2 mutations)

- Adults
- Cardiomyopathy
- Mild limb weakness
- Mental retardation
- Maculopathy

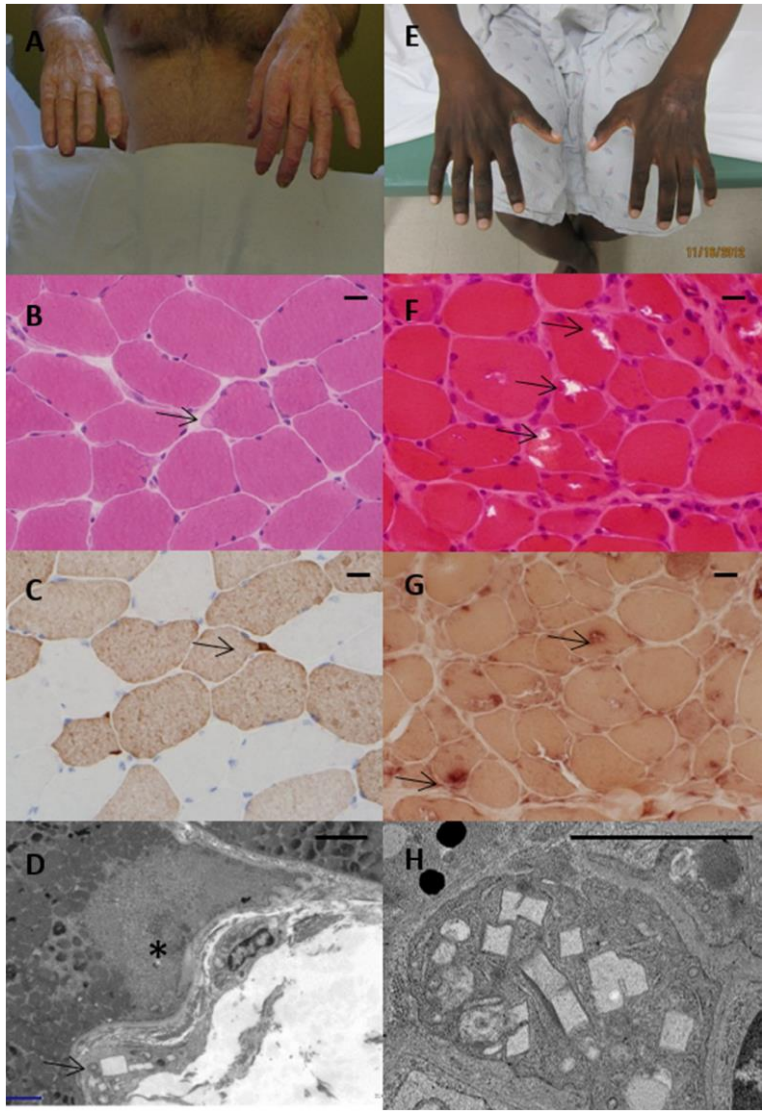


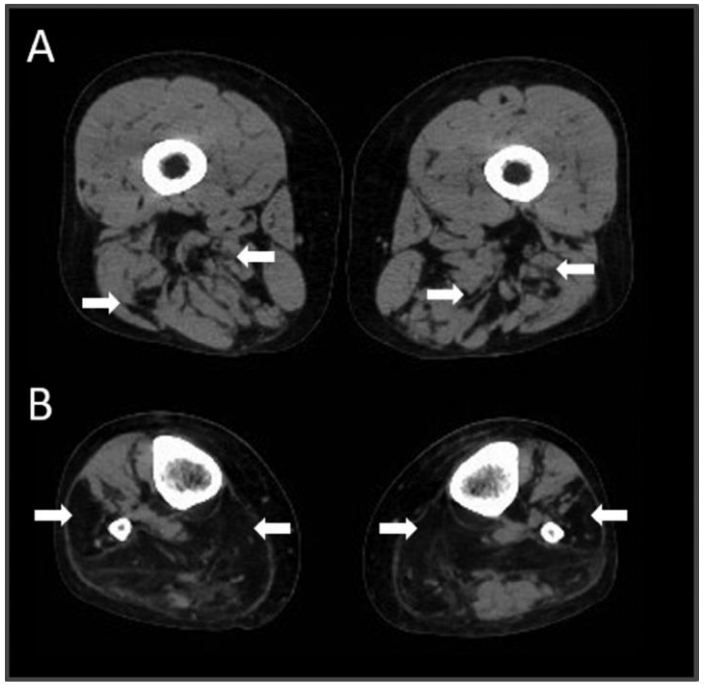
Cystinosis distal myopathy, novel clinical, pathological and genetic features

Macarena Cabrera-Serrano [a,b,*], Reimar C. Junckerstorff [c,d], Ali Alisheri [e], Alan Pestronk [e], Nigel G. Laing [a], Conrad C. Weihl [e], Phillipa J. Lamont [a,f]

Neuromuscular disorders, 2017

- 3 patients from 2 families with nephropathic cystinosis.
- Intrafamiliar variability was detected in one family in which one sibling developed a severe distal myopathy while the other sibling did not show any signs of skeletal muscle involvement.
- One of the patients was on treatment with Cysteamine for over 12 years but still developed the usual complications of nephropathic cystinosis in his twenties





Muscle CT scan of patient 1 at age 55. Fat infiltration involving posterior compartment of thighs (mainly biceps femoris, semitendinous and semimembranous), severe fat infiltration and atrophy of all muscles in posterior compartments of legs including soleus, gastrocnemius and also peroneal muscles, bilaterally. Patchy involvement of tibialis anterior.

Grip Strength in Adults and Children with Cystinosis

Helina Iyob-Tessema[1], Chia-Shi Wang[1], Sabina Kennedy[1], Loretta Reyes[1], Stella Shin[1], Larry A. Greenbaum[1] and Julien Hogan[2,3]

Kidney Int Rep (2021)

- We included 76 patients with a mean grip strength z-score of 2.1 (SD, 1.1), which was lower than seen in patients with CKD without cystinosis
- Among adults, a low level of physical activity was associated with lower grip strength z score.
- A third of the patients reported neuromuscular symptoms, with swallowing issues associated with lower grip strength.
- This impairment is greater in male patients and in patients with late initiation of cysteamine therapy, and is associated with lower physical activity.
- Further studies investigating the effect of different types of physical activities, optimizing cysteamine therapy, and other interventions are needed

Table 4. Comparison of patients' characteristics between patients with and without neuromuscular symptoms

Patient characteristics	Patients with neuromuscular symptoms, n = 24	Patients without neuromuscular symptoms, n = 76	*P* value
Age at diagnosis, mo, median (IQR)	16 (12–23)	18 (12–24)	0.5
Age at cysteamine initiation, mo, median (IQR)	18 (12–30)	18 (13–30)	0.74
Male sex, n (%)	13 (54)	24 (48)	0.62
History of dialysis, n (%)	8 (33)	21 (42)	0.47
History of kidney transplantation, n (%)	16 (67)	32 (64)	0.82
Age at inclusion, yr, median (IQR)	25.0 (12.0–33.0)	26.0 (15.0–32.0)	0.67
Pediatric patients (vs. adults), n (%)	10 (42)	16 (32)	0.41
Type of treatment at inclusion, n (%)			0.78
Immediate release cysteamine[a]	8 (33)	17 (34)	
Delayed release cysteamine[b]	16 (67)	32 (64)	
eGFR at inclusion, ml/min per 1.73 m^2, median (IQR)	48 (32–62)	60 (37–79)	0.28
CKD stage, n (%)			
1	1 (6)	3 (8)	0.12
2	3 (19)	17 (44)	
3A	6 (38)	5 (13)	
3B	2 (13)	10 (26)	
4	4 (25)	4 (10)	

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range.
[a]Immediate release cysteamine (Cystagon; Mylan Pharmaceuticals, Canonsburg, PA).
[b]Delayed release cysteamine (Procysbi; Horizon Therapeutics, Dublin, Ireland).

Recent studies on neuromuscular involvement in cystinosis

Clinical and neurophysiological characterization of early neuromuscular involvement in children and adolescents with nephropathic cystinosis

Nour Elkhateeb[1] · Rasha Selim[2] · Neveen A. Soliman[2] · Fatma M. Atia[2] · Ihab Ibrahim Abouelwoun[3] · Mohamed. A. Elmonem[4] · Rasha Helmy[2]

Pediatric Nephrology, 2022

- Cohort of cystinosis 15 patients (median age 96 months)
- 3 patients had early abnormal neurophysiological features consistent with neuromuscular involvement (clinically asymptomatic proximal myopathy in one patient and isolated asymptomatic sensory nerve conduction changes in two patients).
- A fourth patient had mixed abnormal motor and sensory axonal neuropathic changes associated with overt clinical features (predominantly motor symptoms).
- Patients with abnormal neuromuscular features were significantly older than the unaffected group (P = 0.005) and had a diagnosis of cystinosis with subsequent cysteamine therapy at a significantly older age.
- Prompt diagnosis and timely initiation of cysteamine therapy with recommended dose can delay the development of neuromuscular complications.

Neuromuscular conditions and the impact of cystine-depleting therapy in infantile nephropathic cystinosis: A cross-sectional analysis of 55 patients

Katharina Vill[1] | Wolfgang Müller-Felber[1] | Timotheus Landfarth[2] | Christian Köppl[3] | Nadine Herzig[4] | Christine Knerr[3] | Heike Holla[6] | Günther Steidle[3] | Erik Harms[5] | Katharina Hohenfellner[6] | the Interdisciplinary Cystinosis Group

JIMD, 2022

- Cohort of 55 patients (aged 2.8-41.3 years, median 18.5 years)
- 30% of patients presented with mild, 7% with moderate, and 5% with severe weakness of the intrinsic muscles of the hand
- 28 % of patients had mostly mild axial weakness of the neck flexors and/or of the abdominal rectus muscles
- Neuromuscular complications were largely independent from both the age of initiation of pharmacological cystine-depleting therapy and from adherence to treatment.
- Significant correlation was observed between better physical performance in jumping (mechanography platform) and cystine levels in leukocytes

Oral and swallowing dysfunction in cystinosis

- Sonies *et al.* « Swallowing Dysfunction in Nephropathic Cystinosis ». NEJM, 1990
- Sonies *et al.* « Swallowing Dysfunction in 101 Patients with Nephropathic Cystinosis: Benefit of Long-Term Cysteamine Therapy ». Medicine, 2005
- **Dysfunction of oral motor function:**

  Main structures and functions affected :
  - Word
  - Oral structure and anatomy
  - Tongue strength
  - Lip strength

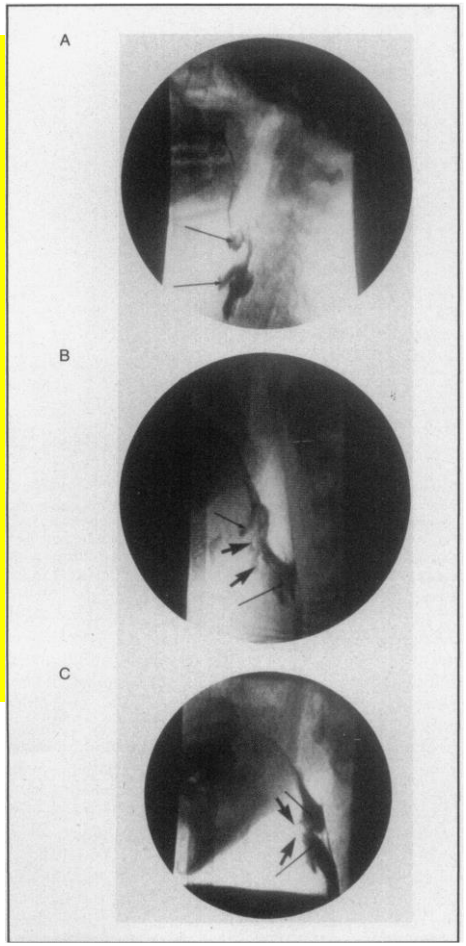
- **Swallowing disorders:**

  Abnormalities of :
  - Oral phase
  - Pharyngeal phase
  - Esophageal phase

→ Generalized impairment of the 3 swallowing phases in renal transplant patients
(Sonies et al., 1990)

Patient complaints :

- Increased difficulty swallowing
- Slow feeding
- Feelings of dry mouth
- Lump in the throat
- Food stuck in cheeks
- Cough
- Choking after swallowing
- Reflux in the oral cavity
- Hoarseness after swallowing
- Exacerbated drooling



Swallowing Dysfunction in 101 Patients with Nephropathic Cystinosis

Benefit of Long-Term Cysteamine Therapy

Barbara C. Sonies, PhD, Phaedra Almajid, MA, MS, Robert Kleta, MD, PhD, Isa Bernardini, MEd, and William A. Gahl, MD, PhD

TABLE 3. Frequency of Dysfunction in the Oral, Pharyngeal, and Esophageal Phases of Swallowing in 101 Patients With Nephropathic Cystinosis, According to Age-Group

	No. With Dysfunction (%)		
Age-Group (yr)	Oral Phase	Pharyngeal Phase	Esophageal Phase
5–15 (n = 17)	3 (18)	3 (18)	8 (47)
16–25 (n = 48)	5 (10)	24 (50)	34 (71)
26–35 (n = 26)	12 (46)	18 (69)	22 (85)
35+ (n = 10)	4 (40)	7 (70)	10 (100)

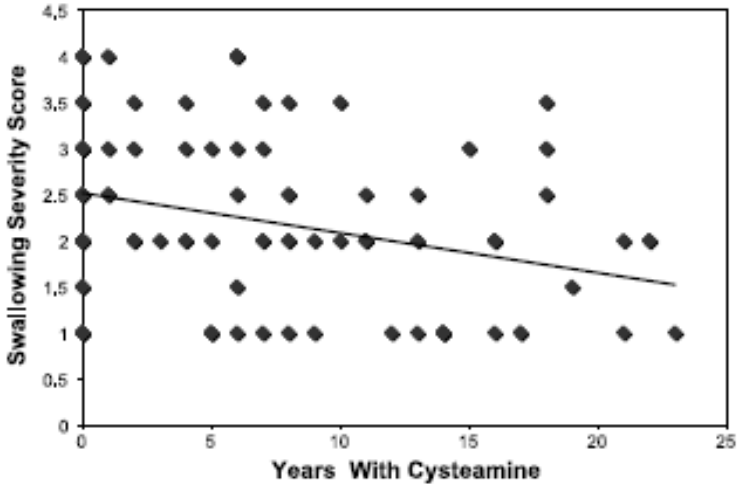


FIGURE 3. Swallowing Severity Score in cystinosis patients in relation to years on cysteamine therapy. Swallowing dysfunction decreased with years on cysteamine according to the equation $y = -0.043x + 2.51$ ($p = 0.0012$).

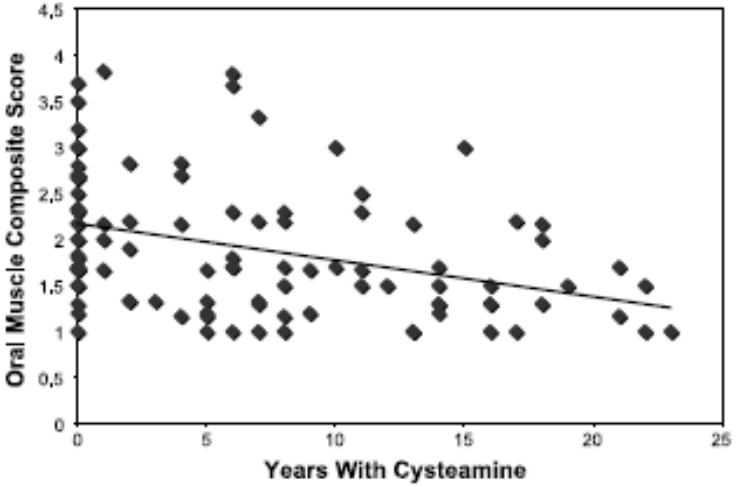


FIGURE 5. Oral Muscle Composite Score in cystinosis patients in relation to years on cysteamine. The equation of the line is $y = -0.04x + 2.13$ ($p = 0.0002$).

Conclusion: Longitudinal studies should be performed to determine whether oral cysteamine therapy preserves or improves swallowing, whether patients treated early with cysteamine do better than those treated later in life, and whether early cysteamine therapy can prevent swallowing difficulties altogether.

Respiratory involvement in cystinosis

- **More frequent in adults with untreated nephropathic cystinosis**
- Extraparenchymal pattern of restrictive lung disease

Characterized by :

↓ **Respiratory muscle strength**	↓ **Respiratory muscle endurance**
Collapse of maximum inspiratory (MIP) and expiratory (MEP) pressures	↓ maximal voluntary ventilation (MVV)

Anikster A *et al.,* « Pulmonary Dysfunction in Adults With Nephropathic Cystinosis ». Chest, 2001

Possible causes :

- Conical chest configuration ? → ↓ chest volumes
- Wasting + muscle weakness ? → similar to pulmonary involvement Pompe disease

« Unmet needs » in research and care of neuromuscular complications of cystinosis

- Need to improve knowledge of clinical manifestations and preferentially involved muscles (+/- peripheral nerve ?)
- Natural history studies (rate of progression, correlations with treatments, other predictive factors…)
- Need to reinforce multidisciplinary care with collaborations between nephrologists/paediatricians/neuromuscular centers (« dual follow-up »)
- Need for deciphering the causes of resistance to treatment of skeletal muscle (study of autophagy mechanisms on muscle biopsy ?)

2020: First natural history study of myopathy in nephropatic cystinosis

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

Clinical myopathy in patients with nephropathic cystinosis

Reza Sadjadi MD[1] | Stacey Sullivan SLP[2] | Natalie Grant BA[1] | Susan E. Thomas MD[3] | Maya Doyle MSW, PhD, LCSW[4] | Colleen Hammond RN[5] | Rachel Duong BA[1] | Camille Corre BS/BA[1] | William David MD, PhD[6] | Florian Eichler MD[1]

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

See Editorial on pages 652–653 in this issue.

Clinical trial readiness study of distal myopathy and dysphagia in nephropathic cystinosis

Reza Sadjadi MD[1] | Stacey Sullivan MS, CCC-SLP[2] | Natalie Grant BA[3] | Susan E. Thomas MD[4] | Maya Doyle MSW, PhD, LCSW[5] | Colleen Hammond RN[6] | Camille Corre BS/BA[7] | Nicholas Mello BS[7] | William S. David MD, PhD[1] | Florian Eichler MD[7]

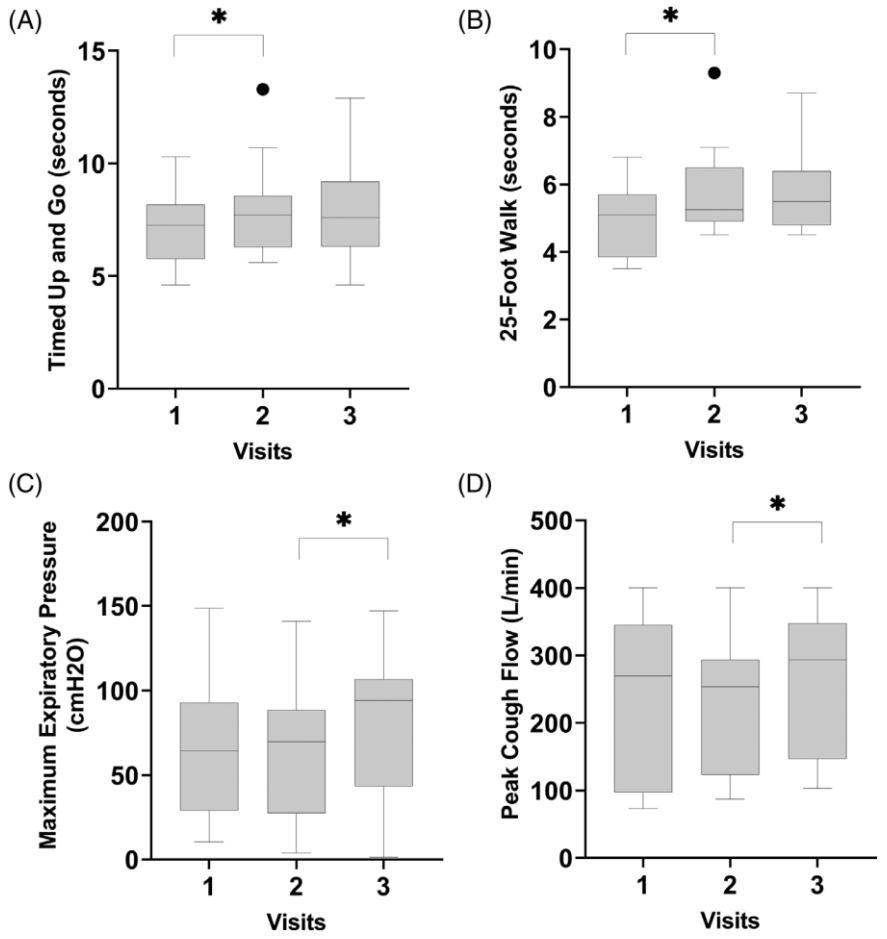
EDITORIAL

See article on pages 681–687 in this issue.

MUSCLE&NERVE

Cystinosis myopathy: Searching for optimal clinical outcome measures

- Evaluation of 20 patients with nephropathic cystinosis in two visits over the course of a year to identify outcomes sensitive to detect changes over time.
- Timed Up and Go Test (TUG) and Timed 25-Foot Walk (25-FW) showed significant improvement comparing visit 1 and visit 2, while other measures did not show significant changes.
- The duration of follow-up, 1 year in this study, may not be sufficient to show significant changes in the selected outcome measures in this slowly progressive cystinosis myopathy
- In conclusion, this study did not find optimal outcome measures in cystinosis myopathy and the search will need to continue. Muscle magnetic resonance imaging (MRI) is a useful tool in detecting muscle changes in symptomatic patients with late-onset Pompe disease, another lysosomal storage disorder, even in the absence of changes in motor function and patient-reported outcomes.



Improving characterization of neuromuscular involvement in adults with cystinosis

- French collaborative project funded in 2022 by the Cystinosis Research Foundation
- Pascal Laforêt, Neurologist, MD, PhD, Raymond Poincaré University Hospital, Garches, France
- Hélène Prigent, Pulmonologist, MD, PhD, Raymond Poincaré University Hospital, Garches, France
- Aude Servais, MD, PhD, Nephrologist, Department of Nephrology and Transplantation, MARHEA reference center, Necker Hospital, Paris Descartes University, Paris, France
- 20 patients followed during one year

French natural history study of cystinosis myopathy: aims

- Systematic neurological examination including standardized assessments of muscle weakness, whole-body muscle MRI, and pulmonary function tests will be performed in a cohort of 20 cystinosis patients.
- Analyze of the swallowing function in patients complaining of swallowing difficulties, or with significant impairment rating after having completed the Sidney Swallow questionnaire. Patients reporting oral symptoms and swallowing difficulties will be referred to ENT specialist with a large experience of neuromuscular diseases (Pr Jean Lacau-Saint Guily
- Clinical and morphological neuromuscular complications will be correlated with the other complications of the disease, renal function or transplantation, leukocyte cystine level, age at initiation of treatment and adhesion to treatment.

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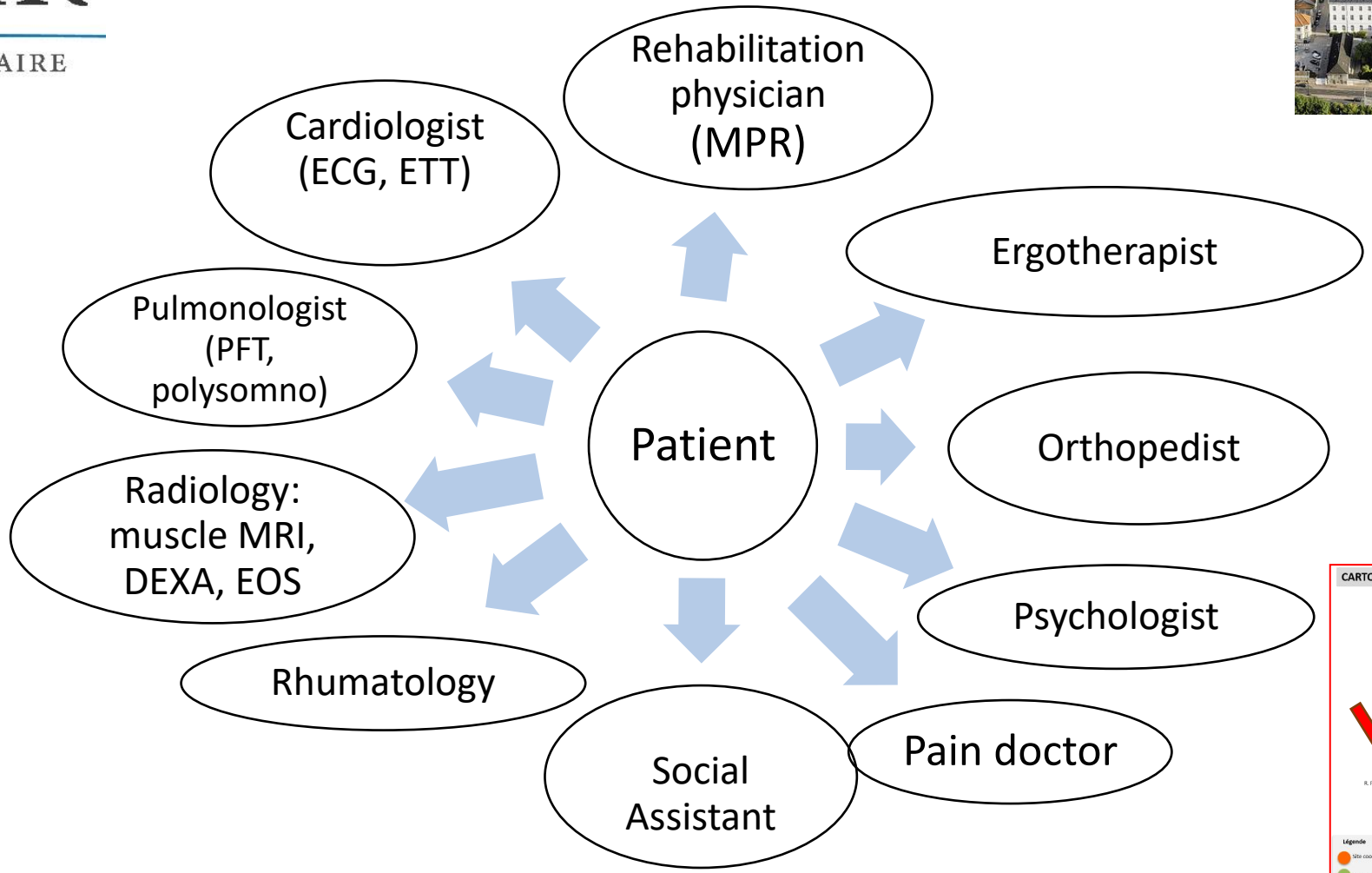
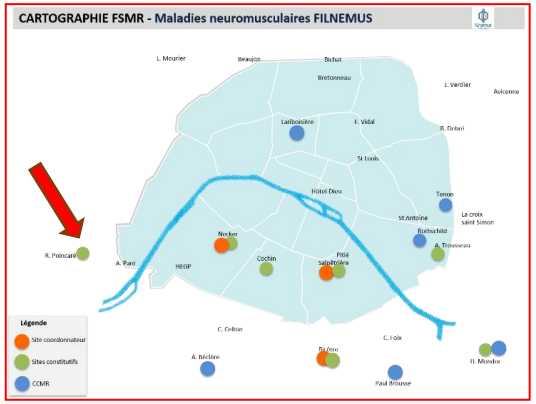
NEUROMUSCULAIRE

Multidisciplinary care of neuromuscular diseases

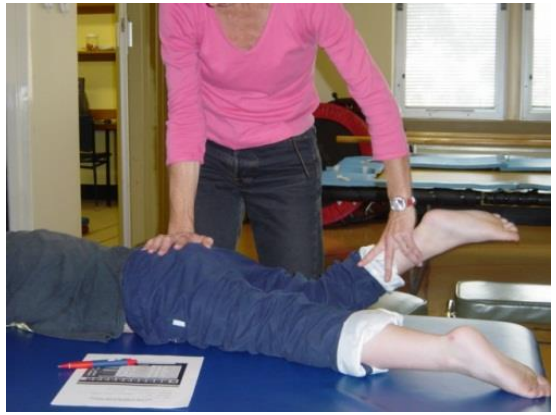




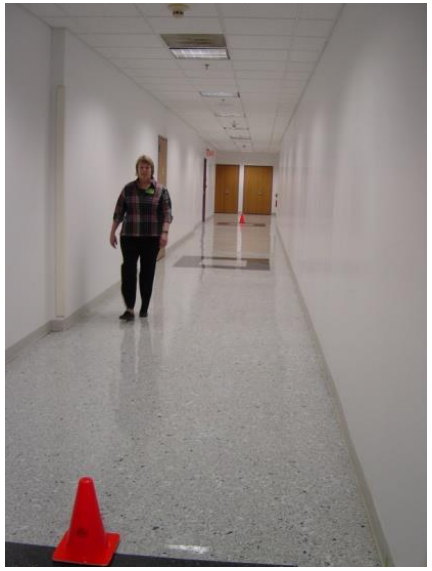
French natural history study design

	V1	V2
Clinical evaluation	X	X
Blood samples	X	X
Mean leucocyte cystine level	X	X
DEXA	X	X
Muscle function evalutation		
• Manual muscle testing	X	X
• Motor Function Measure	X	X
• 6 minutes walking test	X	X
• Timed tests	X	X
• Handgrip dynamometry	X	X
• Distal motor function	X	X
Muscle MRI Imaging	X	-
Respiratory Evaluation		
• Pulmonary function test	X	X
• Blood gases	X	X
• Non-invasive respiratory muscle evaluation	X	X
• Transdiaphramatic pressures	X	-
• Polysomnograpy + capnography	X	X *(only if symptomatic or significant degradation of respiratory function)*

Muscle function analysis



Manual muscle testing

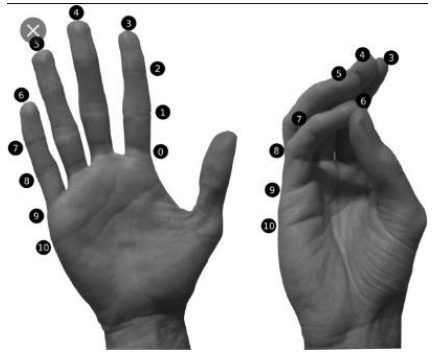


6 minutes walk test

MFM-32 scale: axial, proximal and distal scores

Timed tests

Myotools: handgrip and keypinch

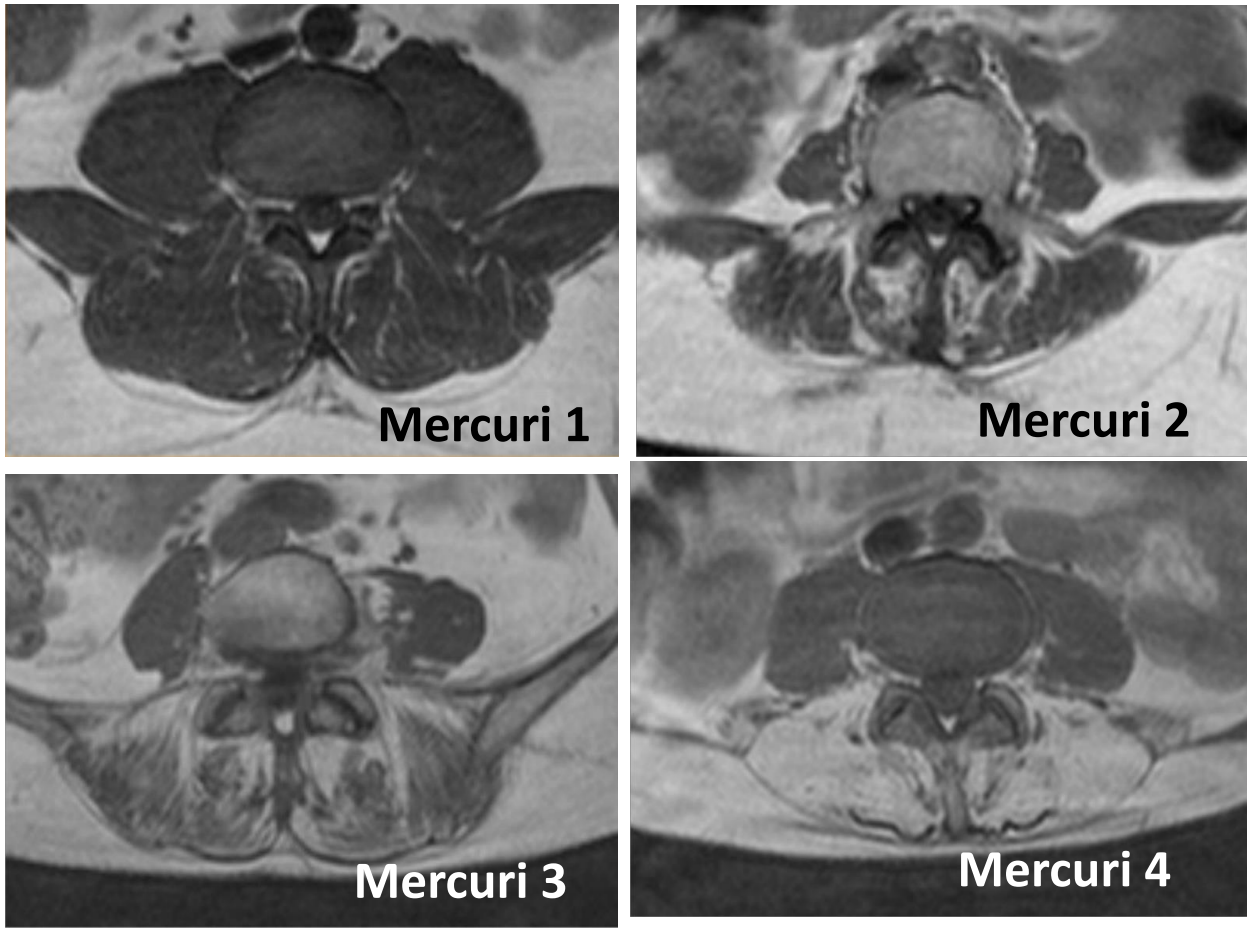


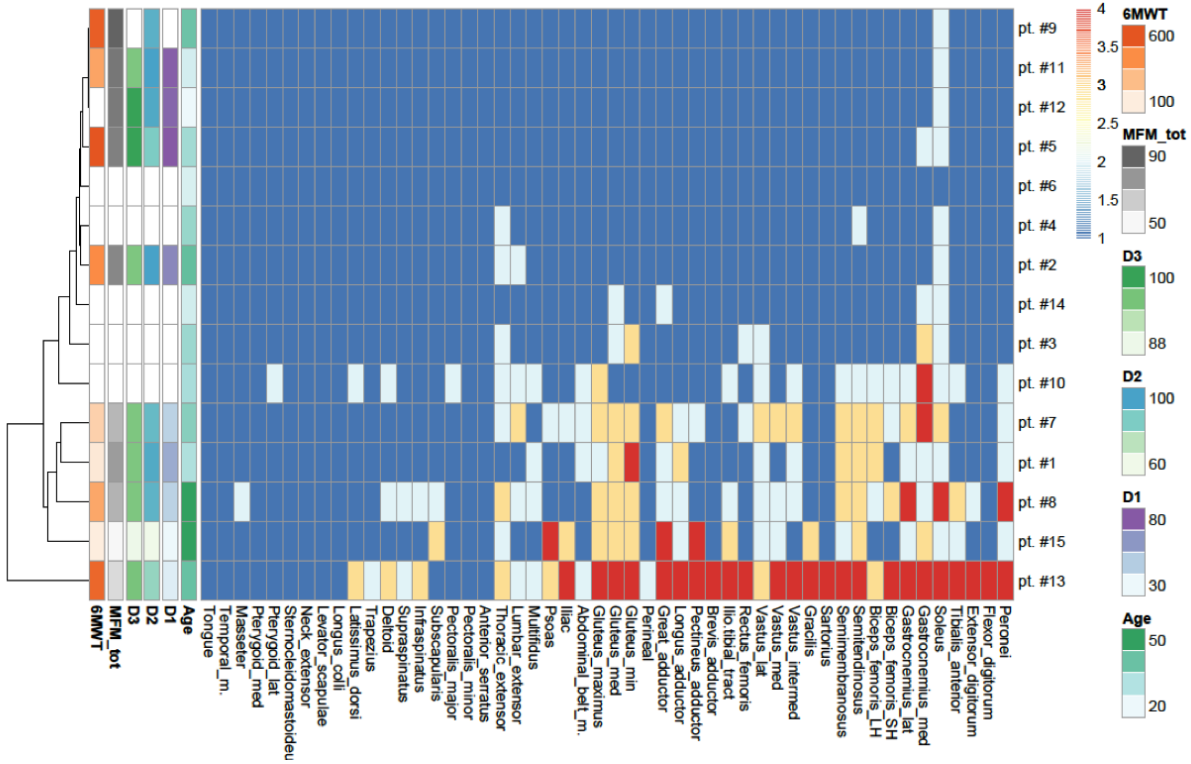
Kapandji test

Purdue pegboard test

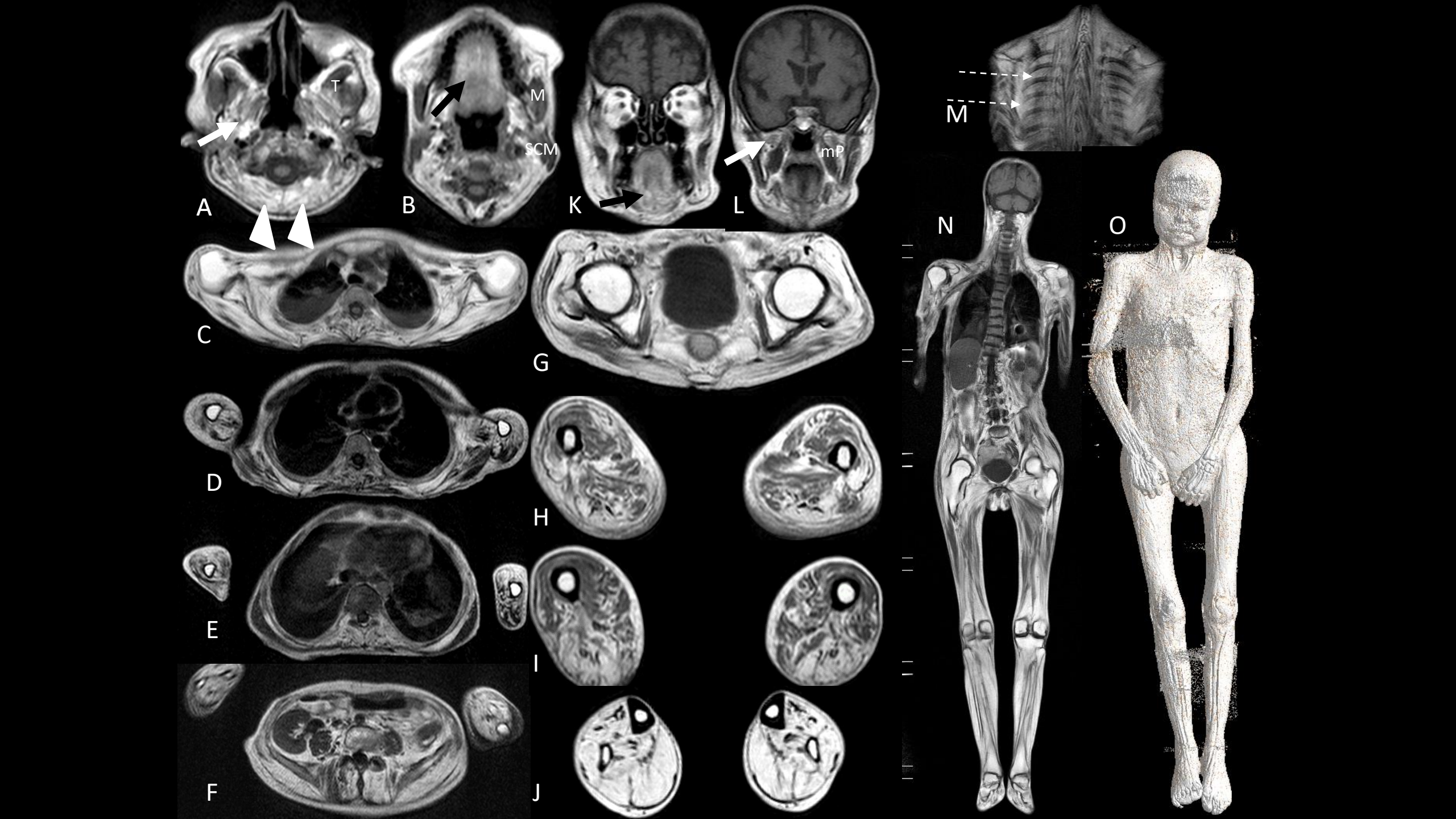
Muscle imaging: whole-body muscle MRI and DEXA

- To characterize muscle involvement, muscle signal intensity and grade of involvement will be ranked from 1 to 4 in all muscles, as described by Mercuri *et al.*
- DEXA will explore the repartition of lean mass, fat and bone mineral content for all body





Heatmap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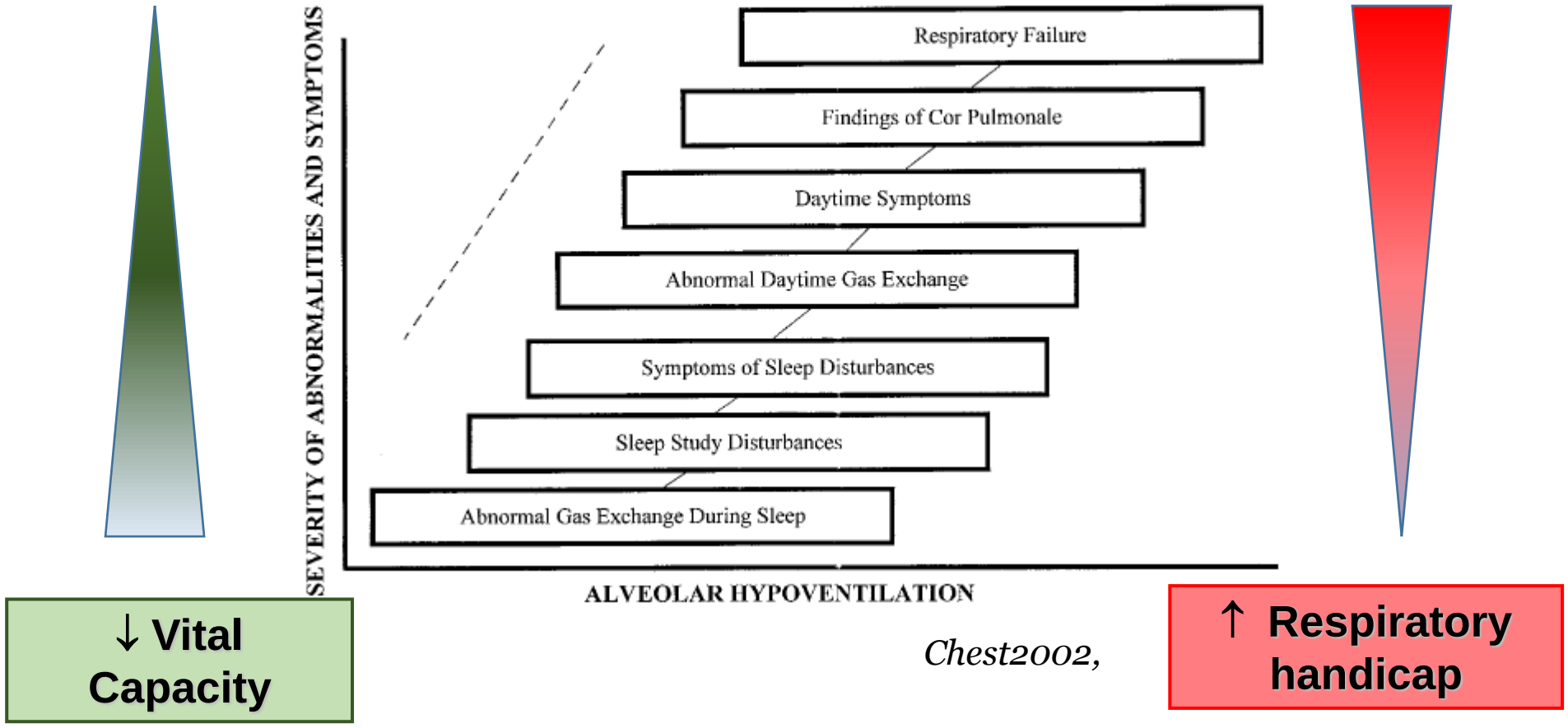
Neuromuscular respiratory insufficiency



Chest2002,

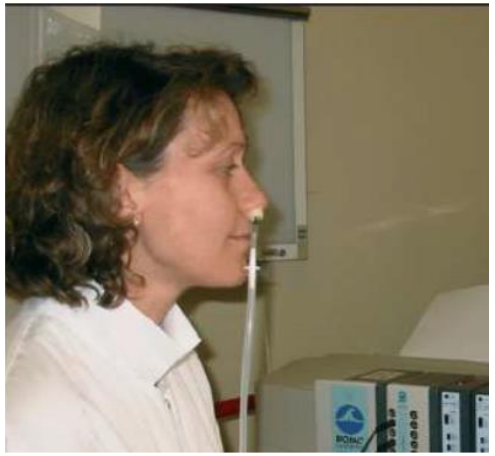
Courtesy: Pr H Prigent, Raymond Poincaré hospital

Respiratory function: 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)



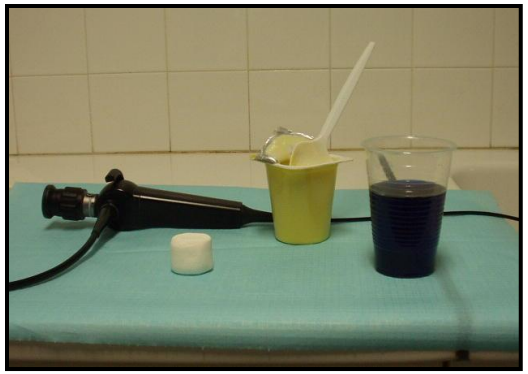
- Respiratory polygraphy or polysomnography:
  - Hypoventilation ++
  - Hypopnea/central apnea and/or obstructive,
  - mixed syndromes

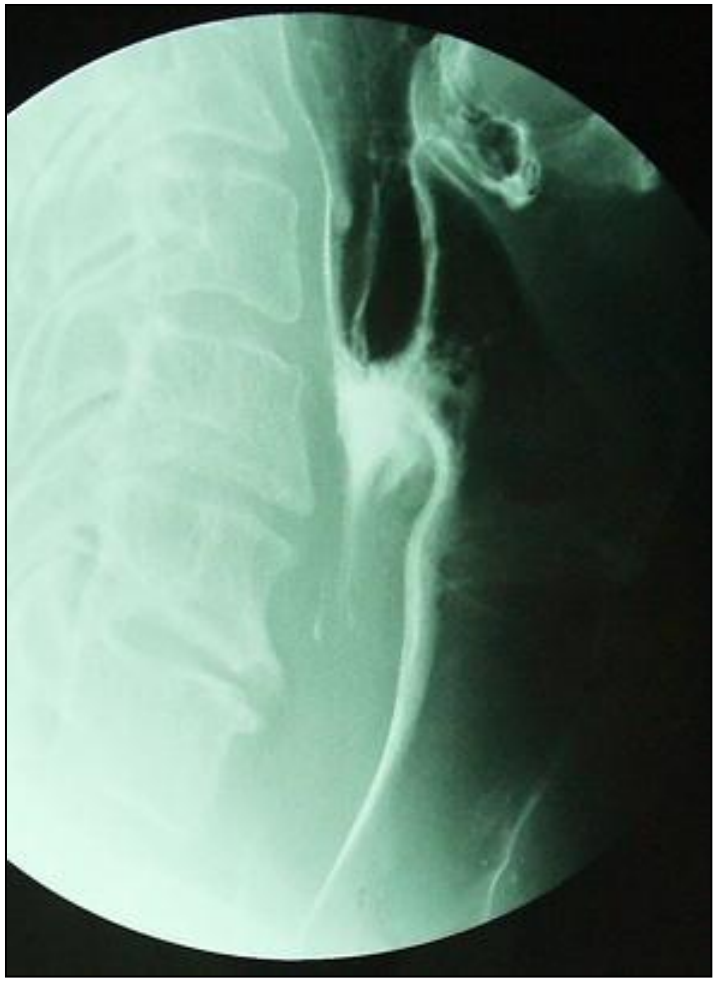
Courtesy: Pr H Prigent, Raymond Poincaré hospital

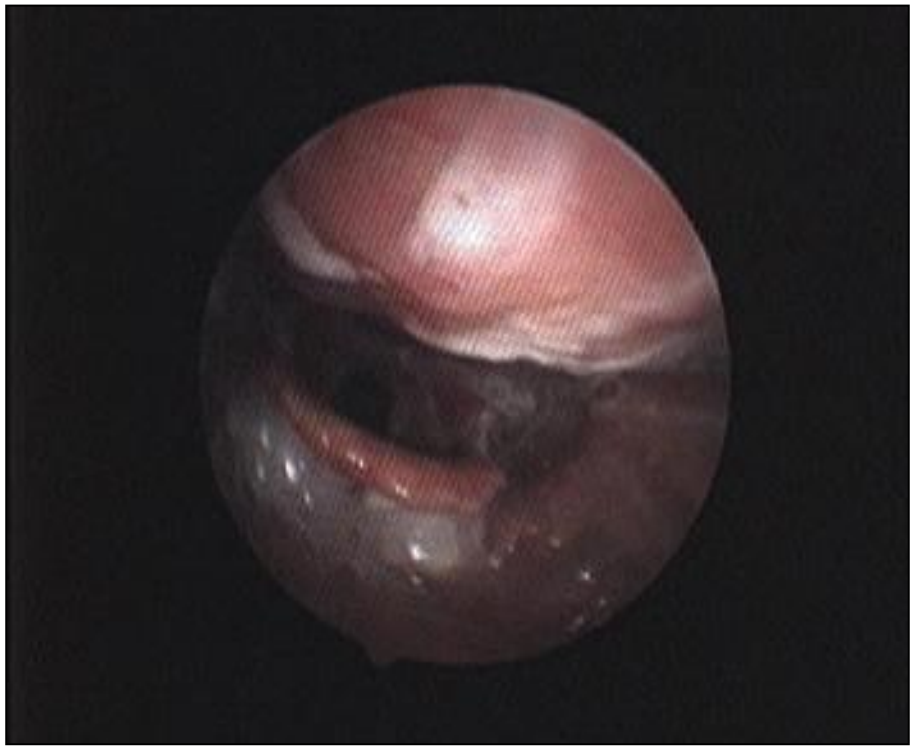
Swallowing assessment

- Clinical symptoms will be evaluated by the Salassa and McHorney scores
- Drink test (time of swallowing 80ml of water; normal =3-4 sec)
- A validated French version of the Sidney Swallow questionnaire will be performed .
- In patients with clinical symptoms and/or significant impairment of the scores, further explorations will be proposed (Pr Jean Lacau St Guily, Fondation Rothschild)):

- Otolaryngological standard examination with naso-laryngoscopy (outpatient procedure)
- Videoendoscopic swallowing study (VESS) using a flexible laryngoscope and a video recording. It includes a morphological study of the pharynx, and a functional assessment of deglutition during dry, thick cream, water swallowing.
- Videofluoroscopy of swallowing , based on a modification of the barium swallowing procedure to assess pharyngeal, Upper esophageal sphincter (UES) function. The images are obtained in lateral and postero anterior positions







Pr Jean Lacau Saint Guily
Fondation Rothschild

French study: anticipated results

- This exploratory study of all dimensions of neuromuscular involvement in patients with cystinosis should provide new insights on pattern, severity and determinants of neuromuscular complications of this lysosomal disease, and help improving care for patients.
- This study could also pave the way for a larger natural history study of neuromuscular manifestations, and to set up outcomes measures which could be used in future clinical trials to assess the response of skeletal muscles to innovative therapies.
- The extensive functional motor and respiratory evaluation, with the systematic intervention of a pulmonologist and an occupational therapist, can lead to propose personalized rehabilitation support and care for patients, and then providing guidelines for detection and assessment of neuromuscular manifestations in cystinosis.

Thank you for your attention !

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