Atelier Pratique en Médecine Interne

SUR LES MALADIES RARES

Actualités maladies rares lysosomales: les maladies rares au service du diagnostic clinique du quotidien

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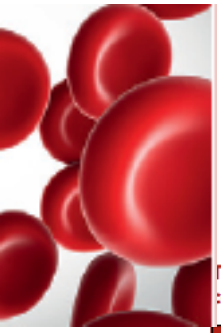
Ateliers Pratiques de l'Interniste, Grenoble
SNFMI, Jeudi 13 décembre 2018

Conflits d'intérêt

- Sanofi-Genzyme, Shire-HGT, Amicus Therapeutics, Actelion, Octapharma, CSL-Behring, LFB, MSD, Roche Chugaï, GSK, Sandoz, Novartis

MALADIE DE GAUCHER/MGUS



How I manage monoclonal gammopathy of undetermined significance

How I Treat

Ronald S. Go and S. Vincent Rajkumar

(*Blood*. 2018;131(2):163-173)

Table 2. Nonmalignant diseases associated with monoclonal gammopathy of undetermined significance and may respond to lymphoplasmacytic cell-directed therapy

Primary organ involved	Clinical presentation	Role of monoclonal protein/pathophysiology	Reference
Dermatologic			
Acquired C1 inhibitor deficiency	Recurrent angioedema without urticaria or pruritus	Antibody to C1 esterase inhibitor	69
Cryoglobulinemia	Acrocyanosis, purpura, cutaneous ulcer, peripheral neuropathy, arthralgia, glomerulonephritis	Immunoglobulin precipitation or antibody binding to antigens causing hyperviscosity or vasculitis	70
Necrobiotic xanthogranuloma	Yellow-orange papules/plaques with frequent ulcerations; may have proptosis and cardiopulmonary involvement	Unclear	71
Schnitzler syndrome	Chronic urticaria, fever, bone pain, IgM-MGUS	Unclear	72
Endocrinologic			
Insulin autoimmune syndrome	Episodic confusion, diaphoresis, dizziness, lethargy, palpitation, seizure	Antibody to insulin causing its inactivation	73
Hematologic			
Acquired von Willebrand syndrome	Easy bruising, mucosal bleeding; may have soft tissue bleeding due to decreased factor 8 level	Antibody to von Willebrand factor causing its clearance or interference with platelet or collagen binding	74
Cold agglutinin disease	Acrocyanosis, $C3^+$ autoimmune hemolytic anemia, red cell agglutination, mostly IgMκ-MGUS	Antibody to red cell I antigen-causing agglutination and hemolysis	75
TEMPI	Telangiectasias, erythrocytosis, elevated erythropoietin level, MGUS, perinephric fluid collections, and intrapulmonary shunting	Unclear	76
Rheumatologic			
Scleromyxedema	Waxy papules or plaques, arthralgia, restrictive lung disease, seizure	Unclear	77
Nephrologic			
Antiglomerular basement membrane disease	Hematuria, proteinuria	Antibody to glomerular basement membrane	78
C3 glomerulonephritis	Hematuria, proteinuria	Antibody to C3 convertase or complement factors B, H, or I causing C3 deposition in glomeruli	79
Dense deposit disease	Hematuria, proteinuria	Antibody to C3 convertase or complement factors B, H, or I causing C3 deposition in glomeruli	80
Fibrillary glomerulonephritis	Hematuria, proteinuria, renal impairment, mostly IgG-MGUS	Fibrillary deposition of immunoglobulin in glomeruli	81
Immunotactoid glomerulonephritis	Hematuria, hypertension, proteinuria, renal impairment, IgG-MGUS	Microtubular deposition of immunoglobulin in glomeruli	82
Light-chain proximal tubulopathy	Aminoaciduria, hyperphosphaturia, normoglycemic glycosuria, proximal renal tubular acidosis, uricosuria, mostly κ-MGUS	Direct light-chain toxicity to proximal renal tubules	83
Membranous nephropathy	IgG3κ-MGUS	Antibody to phospholipase A2 receptor	84
Monoclonal immunoglobulin deposition disease	Hematuria, hypertension, proteinuria, renal impairment, mostly κ-MGUS	Granular deposition of immunoglobulin in glomeruli	85
Progressive glomerulonephritis with monoclonal immunoglobulin deposits	Hematuria, hypertension, proteinuria, renal impairment, mostly IgG3κ-MGUS	Granular deposition of immunoglobulin in glomeruli	86
Neurologic			
CANOMAD	Chronic ataxic neuropathy, ophthalmoplegia, IgM-MGUS, cold agglutinin, and disialosyl antibodies	Antibody to disialosyl ganglioside	87
POEMS	Polyneuropathy, organomegaly, endocrinopathy, mostly λ-MGUS, skin changes	Unclear	88
Primary organ involved	**Clinical presentation**	**Role of monoclonal protein/pathophysiology**	**Reference**
Ophthalmologic			
Corneal copper deposition	Decreased visual acuity, diffuse brownish discoloration of cornea, hypercupremia, IgG-MGUS	Corneal deposition of antibody with strong affinity to copper	90
Crystalline keratopathy	Decreased visual acuity, corneal opacity, IgGκ-MGUS	Corneal deposition of antibody forming a crystalline structure	91
Other			
Capillary leak syndrome	Recurrent hypovolemic shock with generalized edema	Unclear	92
Crystal-storing histiocytosis	Mass or tissue infiltration, which may involve the bone marrow, breast, gastrointestinal tract, kidneys, lymph node, skin, or spleen	Accumulation of light-chain crystals in histiocytes	93

TO THE EDITOR:

Letters to *Blood*

MGUS, lymphoplasmacytic malignancies, and Gaucher disease: the significance of the clinical association

Neal J. Weinreb,[1,2] Pramod K. Mistry,[3] Barry E. Rosenbloom,[4,5] and Madhav V. Dhodapkar[6]

« We ***noticed with some chagrin that GD was not even mentioned*** in a fairly long list of concurrent conditions with wich monoclonal gammopathy of undetermined significance (MGUS) has been associated »

- Association rapportée dès **1968**[1]…
- **Risque relatif de myélome en cas de MG** compris entre **25 et 50**[2]
- **Incidence MGUS 7-16%** (MG) *vs* 1-1,7% population témoin
- Ac spécifiquement dirigés contre macrophage CD1d présentant Ag glycosphingolipidique[3] : **lyso-glucosylceramide (LGL1)**
- Ig monoclonale spécifique pour lysolipide LGL1 et lysophosphatidylcholine (LPC): 33% MG
- Rôle (MG, GM sporadiques) **activation chronique par les lysolipides** +++

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Clonal Immunoglobulin against Lysolipids in the Origin of Myeloma

Shiny Nair, Ph.D., Andrew R. Branagan, M.D., Jun Liu, Ph.D., Chandra Sekhar Boddupalli, Ph.D., Pramod K. Mistry, M.D., and Madhav V. Dhodapkar, M.B., B.S.

[1]Pratt PW, Kochwa S, Estren S. *Blood* 1968
[2]Arends *et al*. *Br J Haematol* 2013
[3]Nair *et al*. *N Engl J Med* 2016

TO THE EDITOR:

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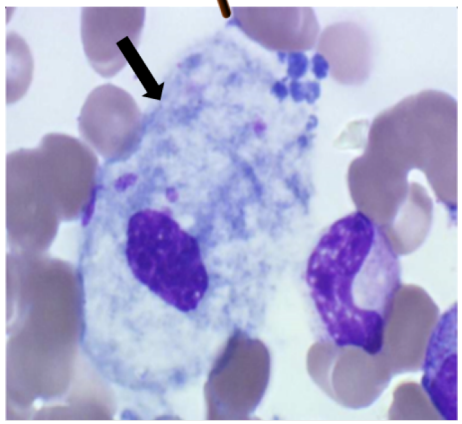
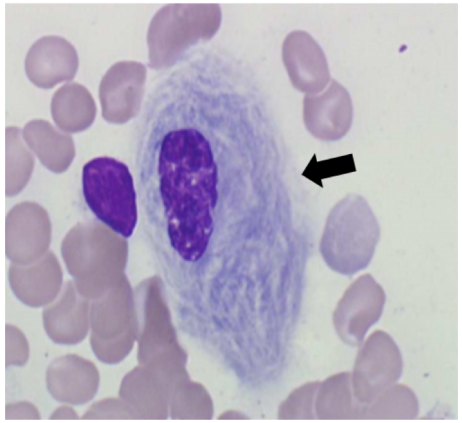
- Thérapie par réduction de substrat améliore la maladie de Gaucher associée à une gammapathie chez les souris
- Pas de réversion d'une GM par l'ERT mais **quid de l'efficacité préventive sur l'émergence clones plasmocytaires** en cas d'initiation précoce ?
- **Accélération risque transformation MGUS en myélome** (1%/an) en cas de co-existence GD-MGUS ?
- **Urgence à renseigner les data bases**

[1]Pratt PW, Kochwa S, Estren S. *Blood* 1968
[2]Arends *et al*. *Br J Haematol* 2013
[3]Nair *et al*. *N Engl J Med* 2016

Quand penser Gaucher en cas de MGUS (et/ou myélome) ?

- **Atteintes osseuses ostéolytiques**
- **Organomégalie**
- **Pseudo-cellules de Gaucher**





➔ Dosage de **glucocérébrosidase**

Remerciements Dr S. Daliphard, Dr C. Lafon

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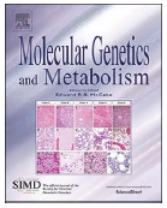


Exploring the patient journey to diagnosis of Gaucher disease from the perspective of 212 patients with Gaucher disease and 16 Gaucher expert physicians **(12 pays, 14 centres experts)**

Atul Mehta[a,*], Nadia Belmatoug[b], Bruno Bembi[c], Patrick Deegan[d], Deborah Elstein[e], Özlem Göker-Alpan[f], Elena Lukina[g], Eugen Mengel[h], Kimitoshi Nakamura[i], Gregory M. Pastores[j], Jordi Pérez-López[k], Ida Schwartz[l,m], Christine Serratrice[n], Jeffrey Szer[o], Ari Zimran[p], Maja Di Rocco[q], Zoya Panahloo[e], David J. Kuter[r], Derralynn Hughes[a]

- **7-15 ans d'errance diagnostique** après la 1ère consultation

↘ 9 années espérance de vie /population générale

- Insuffisance connaissances (54%), hétérogénéité des symptômes (23%), sympt. modérée (15%), tests externalisés ((8%)
- 86% consultent un hématologue ou onco-hémato lors de leurs parcours diagnostique
- Triade : thrombocytopénie-hépatosplénomégalie-douleurs osseuses : myélome multiple pour 22% des hématologues, MG pour 20%[1]
- Signes de début parfois modérés, signes non pathognomoniques
- **Nécessité d'améliorer la connaissance de la maladie** (chez des non-spécialistes)

[1]Mistry *et al*. *Am J Haematol* 2007

Presenting signs and patient co-variables in Gaucher disease: outcome of the Gaucher Early Diagnosis Consensus (GED-C) Delphi initiative

Authors

Atul Mehta,[1] David J. Kuter,[2] Sam S. Salek,[3] Nadia Belmatoug,[4] Bruno Bembi,[5] Jeremy Bright,[6] Stephan vom Dahl,[7] Federica Deodato,[8] Maja Di Rocco,[9] Ozlem Goker-Alpan,[10] Derralynn A. Hughes,[1] Elena A. Lukina,[11] Maciej Machaczka,[12] Eugen Mengel,[13] Aabha Nagral,[14] Kimitoshi Nakamura,[15] Aya Narita,[16] Beatriz Oliveri,[17] Gregory Pastores,[18] Jordi Pérez-López,[19] Uma Ramaswami,[1] Ida V. Schwartz,[20] Jeff Szer,[21] Neal J. Weinreb[22] and Ari Zimran[23].

doi: 10.1111/imj.14156

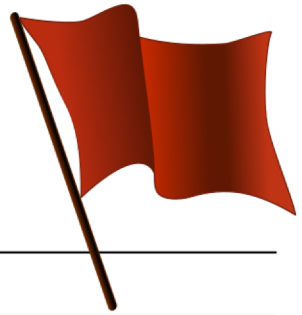
Intern Med J 2018

- **22 experts**
- Expérience médiane 17,5 années
- Suivant 3000 patients
- Méthode **Delphi**
- Échelle de Likert (5-points)

Table 1. **Presenting clinical signs and co-variables in early type 1 GD.**

	Clinical signs	Round 2 Importance score (Likert scale: 1–5)[a]			Round 3 Agreement score (Likert scale: 1–5)[b]		
		Mean score	Median score	Respondents (%)[c]	Mean score	Median score	Respondents (%)[c]
Major	Splenomegaly	4.77	5	100	4.86	5	100
	Thrombocytopenia	4.45	5	95	4.68	5	91
	Bone issues including pain, crises, AVN, and fractures	4.00	4	91	4.45	5	91
	Anaemia	3.77	4	95	4.05	4	86
	Hepatomegaly	3.68	3.5	95	3.95	4	77
	Elevated ferritin levels	3.50	4	82	4.05	4	86
	Gammopathy – monoclonal or polyclonal	3.23	3	82	3.64	4	73
Minor	Bleeding, bruising, or coagulopathy	3.59	4	86	3.68	4	64
	Elevated serum angiotensin-converting enzyme levels	3.18	3.5	64	–	–	–
	Growth retardation including low body weight	3.00	3	73	–	–	–
	Low bone mineral density	2.95	3	59	–	–	–
	Fatigue	2.82	3	64	–	–	–
	Asthenia	2.59	2.5	50	–	–	–
	Leukopenia	2.50	3	55	–	–	–
	Gallstones	2.32	2	45	–	–	–
	Dyslipidemia	2.27	2	36	–	–	–
Discounted	Neonatal cholestasis	1.73	2	9	–	–	–
	Elevated bilirubin levels	1.68	1.5	14	–	–	–
	Co-variables						
Major	Family history of GD	4.27	4.5	95	4.45	5	91
	Jewish ancestry	3.91	4	86	4.18	4	86
Minor	Family history of PD	3.14	3	73	–	–	–

Les 7 signes qui doivent faire évoquer une maladie de Gaucher



Major signs	
Gastroenterological	**Haematological**
Splenomegaly[a]	Anaemia[b]
Hepatomegaly[b]	Thrombocytopenia[b]
	Gammopathy
Orthopaedic	
Bone pain[c]	**Neurological**[d]
Kyphosis	Slow horizontal saccades with unimpaired vision
	Impairment of primary motor development
General medical	Myoclonus epilepsy
Hyperferritinaemia[b]	
Covariables	
Jewish ancestry	Family history of Gaucher disease

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DOI: 10.1002/ajh.25300

WILEY AJH

RESEARCH ARTICLE

Outcomes after 8 years of eliglustat therapy for Gaucher disease type 1: Final results from the Phase 2 trial

Elena Lukina[1] | Nora Watman[2] | Marta Dragosky[3] | Heather Lau[4] | Elsa Avila Arreguin[5] | Hanna Rosenbaum[6] | Ari Zimran[7] | Meredith C. Foster[8] | Sebastiaan J. M. Gaemers[9] | M. Judith Peterschmitt[10]

19 des 26 patients ont été suivis pendant 8 années
Patients MG1 thrombocytopénie et/ou anémie et splénomégalie

Hématologie

Maintien des résultats à 8 ans des résultats obtenus à 1 an (↘ volume rate 59%, ↘ foie 34%, ↗ Hb 2,2 g/dL, ↗plaquettes 113%
Données comparables à celles obtenues après 10 ans d'imiglucérase

Os

T-score lombaire moyen 0,96 (ostéopénie à normal)

Biomarqueurs

Chitotriosidase ↘ 91%, ↘ CCL18 87%, ↘ lyso-GL1 92%, ↘plasma glucosylcéramide (GL1) 80%

Objectifs thérapeutiques, QdV, tolérance

MALADIE DE FABRY

Maladie de Fabry : de nouvelles directives spécifiques actualisées pour les adultes ?

Molecular Genetics and Metabolism 123 (2018) 416–427

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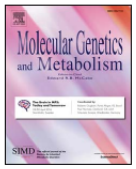


Minireview

Fabry disease revisited: Management and treatment recommendations for adult patients

Alberto Ortiz[a,*], Dominique P. Germain[b], Robert J. Desnick[c], Juan Politei[d], Michael Mauer[e], Alessandro Burlina[f], Christine Eng[g], Robert J. Hopkin[h], Dawn Laney[i], Aleš Linhart[j], Stephen Waldek[k], Eric Wallace[l], Frank Weidemann[m], William R. Wilcox[i]

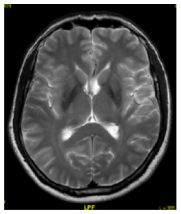
- Maladie de surcharge lysosomale **liée à l'X**, mutations du gène GLA, **déficit activité αGal**
- Accumulation glycosphingolipides et **complications mortelles**
- **Variations phénotypiques** : formes classiques avec début pédiatrique et atteinte multi-organique aux formes d'apparitions tardives majoritairement cardiologiques
- Manifestations diverses chez les femmes (hétérozygotes) : variations activité enzymatique résiduelle et schémas d'**inactivation du chromosome X**
- Enzymothérapie et traitements adjuvants potentiellement à l'origine d'amélioration clinique
- données disponibles pour des patients vus tardivement
- **15 années d'enzymothérapie**
- Guidelines actualisées disponibles pour les enfants[1]
- Groupe « expert », meetings Atlanta 2014/Orlando 2015

[1]Hopkin *et al*. *Mol Genet Meta*b 2016

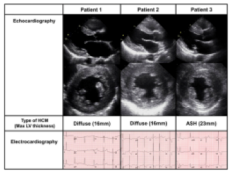
La maladie de Fabry : une maladie systémique

Atteintes neurocentrales et vasculaires

- AVC sujet jeunes
- Pulvinar

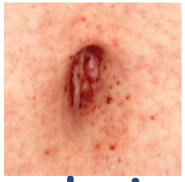


Atteintes cardiaques



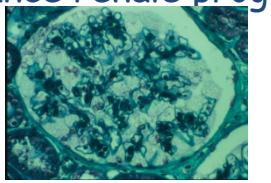
Atteintes dermatologiques

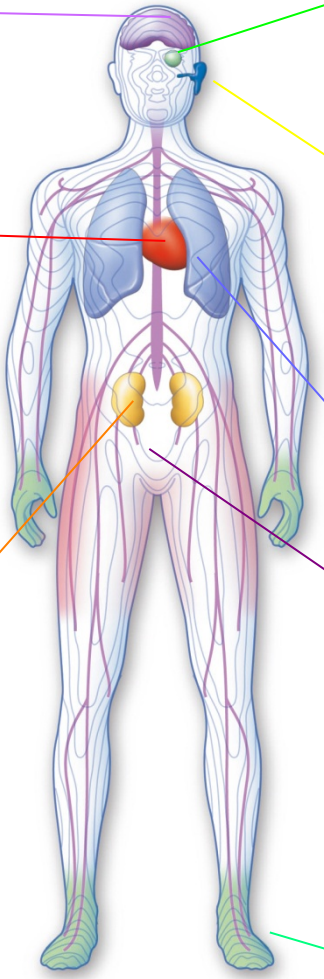
- Angiokératomes
- **anhidrose**
- Lymphoedème



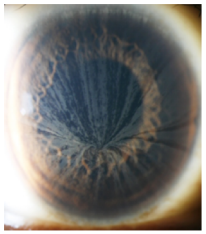
Atteintes néphrologiques

- Protéinurie précoce
- Insuffisance rénale progressive tardive





Atteintes ophtalmologiques



Atteintes ORL

- Hypoacousie, surdités
- Acouphènes
- Vertiges

Atteintes pulmonaires

Atteintes gastro-intestinales

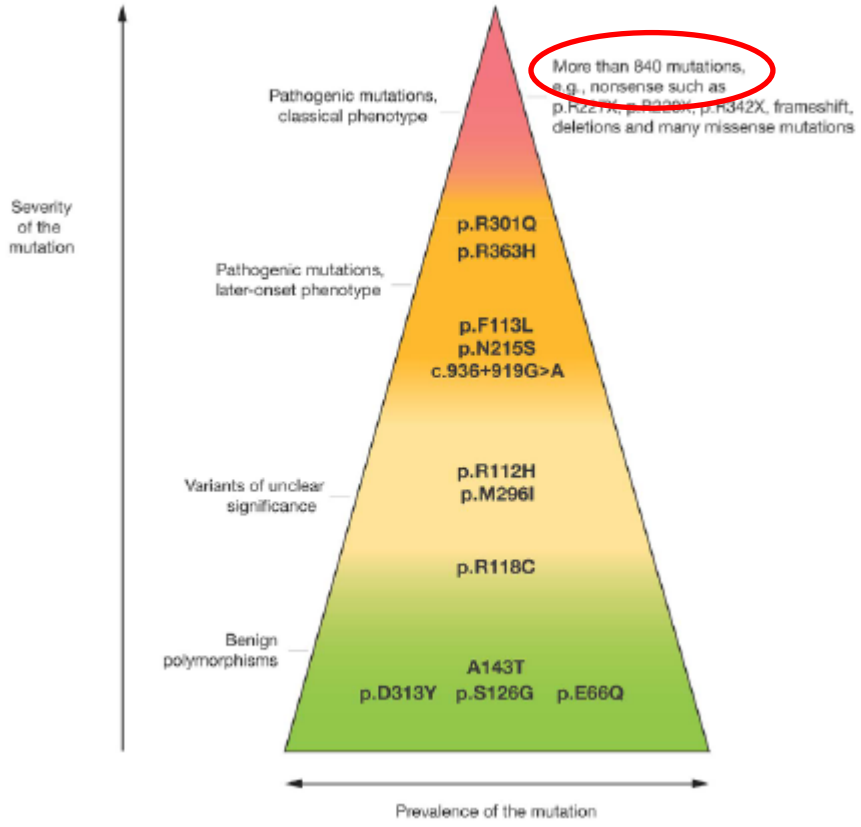
Atteinte osseuse

- Ostéopénie
- Ostéoporose

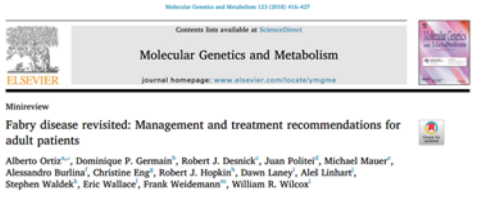
Atteintes neurologiques

- Acroparesthésies

Génotypes: *quid novi* ?



- **Mutations associées au phénotype classique** :
  - non-sens, décalage du cadre de lecture, site d'épissage
  - **Activité résiduelle αGal faible ou nulle**
- **Mutations** faux-sens, rares mutations du site d'épissage
  - **Activité résiduelle αGal**
  - **Phénotypes « late-onset »**
- Biais d'inactivation du X
  - Facteur de variabilité phénotypique femmes hétérozygotes
- ***VUS*** : variants de signification indéterminée
- Confrontation nécessaire génotype avec clinique, biologie, données tissulaires


Molecular Genetics and Metabolism

Minireview

Fabry disease revisited: Management and treatment recommendations for adult patients

Initiations de l'enzymothérapie : recommandantions✓

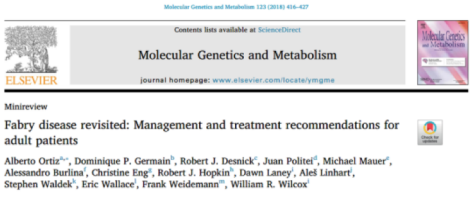
Adult patient population	Recommendation for the initiation of ERT
Classic Fabry mutation	
• Male patient, symptomatic or asymptomatic ✓	• ERT should be considered and is appropriate in all patients at any age of presentation[a]
• Female patient, symptomatic ✓	• Signs/symptoms suggesting major organ involvement, warranting initiation of ERT - neuropathic pain, pain crises, Fabry disease neuropathy - proteinuria/albuminuria NOT attributable to other causes, evidence of renal impairment (may require renal biopsy if isolated) - stroke or TIA - symptomatic cardiac disease not due to other causes (dyspnea, palpitations, syncope, chest pain) - recurrent diarrhea, chronic, disabling GI dysfunction (excluding alternative causes) - exercise intolerance and impaired sweating
• Female patient, asymptomatic[b] ✓	• ERT should be considered if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS - renal disease: decreased GFR (< 90 mL/min/1.73 m^2 adjusted for age > 40 years [GFR category ≥ G2], persistent albuminuria > 30 mg/g [albuminuria category A2 or A3]), podocyte foot process effacement or glomerulosclerosis on renal biopsy, moderate or severe GL-3 inclusions in a range of renal cell types - silent strokes, cerebral white matter lesions (on brain MRI)[c] - asymptomatic cardiac disease (cardiomyopathy or arrhythmia, cardiac fibrosis on contrast cardiac MRI) • ERT should also be considered if a skewed X chromosome inactivation pattern with predominant expression of the mutant *GLA* allele with or without very low α-Gal A activity have been demonstrated in the presence of signs and symptoms of disease
Later-onset Fabry mutation or missense *GLA* VUS	
• Male and female patients	• ERT should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS, as detailed above, even in the absence of typical Fabry symptoms. The abnormalities should be attributable to Fabry disease; this may require histological assessment or biochemical evidence of GL-3 accumulation • The advice of an expert in genetics and management of Fabry disease should be sought for interpretation of the pathogenicity of any VUS • Individuals with well characterized benign *GLA* polymorphisms should not be treated with ERT • In the absence of demonstrable Fabry disease-related tissue pathology or clinical symptoms, ERT may not be appropriate, particularly in heterozygous female patients. These patients should be monitored regularly by a multidisciplinary care team

CNS, central nervous system; ERT, enzyme replacement therapy; α-Gal A, α-galactosidase A; GFR, glomerular filtration rate; GI, gastrointestinal; GL-3, globotriaosylceramide; MRI, magnetic resonance imaging; TIA, transient ischemic attack; VUS, variant of unknown significance.

[a] Treatment decisions may be influenced by advanced elderly age of the patient and severe comorbidity.

[b] Treatment decisions in female patients may be guided by the X chromosome inactivation profile, if assessed. Predominant expression of the mutant *GLA* allele is generally associated with rapid disease progression, requiring closer monitoring and early therapeutic intervention [6].

[c] See also online Appendix D.

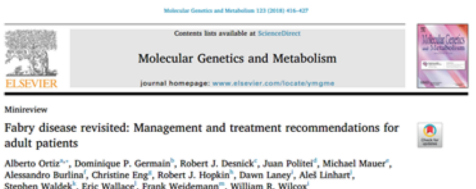


Traitements adjuvants/symptomatiques et prévention

Organ/system	Adjunctive/symptomatic therapy and preventative measures
General	• Genetic counseling (at diagnosis and at adolescence/pre-pregnancy, during pregnancy, or periodically for new issues) [20]
Renal	• Standard management approach for CKD - ACEI or ARB to target albuminuria level < 30 mg/g creatinine if baseline 30–300 mg/g or < 300 mg/g if baseline > 300 mg/g (roughly equivalent to proteinuria > 500 mg/g); great care should be taken if patient has baseline hypotension; dietary salt restriction - general management of CKD regarding statin indication and CKD-MBD prevention and management according to guidelines [87–90] - consider assessment of 25 OH vitamin D levels and replacement therapy if deficient [87] - dialysis or kidney transplantation for patients entering renal failure (donor screened negative for Fabry disease if living related)
Cardiac	• Consider ACEI or ARB; beta blockers should be used with caution and amiodarone avoided in patients receiving ERT[a] • If symptomatic bradycardia/chronotropic incompetence or significant AV conduction impairment, consider permanent cardiac pacing • If evidence of atrial fibrillation, lifetime anticoagulation should be initiated, maintenance of sinus rhythm should be preferred while the use of amiodarone should be avoided, if possible • If evidence or strong suspicion of malignant arrhythmias, consider implantable cardioverter-defibrillator
Cerebrovascular	• Stroke prophylaxis with antithrombotic agents (aspirin or clopidogrel) is indicated as secondary prevention; no data are currently available regarding primary prevention • Stroke prophylaxis with anticoagulants (warfarin or the new anticoagulant drugs in absence of kidney failure), when needed, e.g., patients with atrial fibrillation [17]
Peripheral nervous system	• Individualize strategy for neuropathic pain management • First-line agents include anticonvulsants (e.g., carbamazepine, gabapentin, pregabalin); other drugs can be considered according to current international recommendations for neuropathic pain [19] • Pain crises: consider opioid agonists (care needed to avoid worsening GI disturbances) [19] • Avoid pain triggers with lifestyle modifications (e.g., avoid temperature extremes, maintain proper hydration, use air conditioning, cooling vests, facial mist/spray) [19]
Gastrointestinal	• Delayed gastric emptying and dyspepsia symptoms may be successfully treated with metoclopramide and H-2 blockers, respectively; dysmotility and diarrhea may be treatable with dietary changes (increased fiber intake, more frequent and smaller meals) and pharmacotherapy
Pulmonary	• Bronchodilators to provide relief of airway obstruction
Ophthalmological	• Polarized glasses can help manage difficulty in driving at night (headlight splaying); artificial tears ointment
Auditory	• Hearing aids, cochlear implants
Dermatological	• Laser/cosmetic treatment for angiokeratomas not proven effective; compression stockings can improve lymphedema

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; AV, atrioventricular; CKD, chronic kidney disease; GI, gastrointestinal; MBD, metabolic bone disorder.

[a] The use of beta blockers requires careful monitoring due to the risk of bradycardia exacerbation and chronotropic incompetence. The use of amiodarone should also be limited, as it may have an inhibitory effect on α-GAL activity. See also online Appendix B, Section 3.2.


Molecular Genetics and Metabolism

Minireview

Fabry disease revisited: Management and treatment recommendations for adult patients

Surveillance: évaluation/calendrier

Organ/system	Assessment(s)	Monitoring schedule
General	Complete history and physical examination including family history and evaluation of quality of life [94], gastrointestinal symptoms, work/study performance, level of depression/anxiety	Every clinic visit
	α-Gal A enzyme activity and *GLA* mutation analysis	If not previously determined
Renal	Glomerular filtration rate (measured GFR [preferred] or estimated [eGFR] using appropriate formulae)	Annually if low risk, every 6 months if moderate risk, and every 3 months if high to very high risk;[a] measured GFR only once yearly because of complexity
	Albuminuria (preferred, more sensitive) and/or proteinuria (24-h or spot urine for total protein/creatinine and albumin/creatinine ratios)	Annually if low risk, every 6 months if moderate risk, and every 3 months if high to very high risk
	25 OH vitamin D	As clinically indicated; vitamin D levels in late fall/early winter
	Kidney biopsy	As clinically indicated. Podocyte foot process effacement may precede pathological albuminuria
Cardiac	Blood pressure and cardiac rhythm	Every clinic visit
	ECG and echocardiography	Annually, and as clinically indicated
	48-h Holter monitoring to detect intermittent rhythm abnormalities; [95] implantable loop recorder recommended for patients with significant hypertrophic cardiomyopathy [96]	Annually, but may be assessed more or less frequently depending on age and other risk factors; if arrhythmias detected, more frequent/detailed rhythm surveillance should be instituted (schedule determined individually)
	Cardiac MRI with gadolinium	If available, whenever there is evidence of clinical progression of disease or regularly at an interval > 2 years
	Cardiac MRI with T1 mapping	Investigational tool, should be interpreted with caution
	Brain natriuretic peptide	At least annually for patients with cardiomyopathy or bradycardia
Cerebrovascular	Brain MRI (TOF MRA at first assessment in male patients aged over 21 and female patients over 30, then according to the clinical picture)	Every 3 years and when clinically needed (e.g., presence of neurological changes that could potentially relate to stroke) [37]
	CT imaging	In case of acute stroke and only if MRI is contraindicated due to cardiac pacing
Peripheral nervous system	Pain evaluation and history: pain measurement scale such as the Neuropathic Pain Symptom Inventory or Brief Pain Inventory	Annually
	Cold and heat intolerance, vibratory thresholds (quantitative sensory testing, if available)	Annually (less frequently in older patients)
	Autonomic symptom evaluation by orthostatic blood pressure	Annually
	Skin biopsy (for IENFD assessment, if available)	Consider
ENT	Audiometry [17]	As required [17]
Pulmonary	Spirometry, including response to bronchodilators, treadmill exercise testing, oximetry, chest X-ray	Every 2 years or more frequently for clinical indications; [17] chest X-ray according to clinical indications
Gastrointestinal	Referral to gastroenterology specialist for endoscopic or radiographic evaluation	If symptoms persist or worsen despite treatment
Overall glycolipid burden	Plasma and urinary sediment lyso-GL-3, GL-3	At baseline and then annually (at the moment, this is for research purposes only); biobanking of plasma/serum samples recommended if feasible
Skeletal	Bone dual-energy X-ray absorptiometry (DEXA)	Consider
Ophthalmological	Ophthalmological screening	Ophthalmological screening as clinically indicated

Annuel _____ Points particuliers _____ ✓ clinique

Surveillance: évaluation/calendrier

Organ/system	Assessment(s)	Monitoring schedule
General	Complete history and physical examination including family history and evaluation of quality of life [94], gastrointestinal symptoms, work/study performance, level of depression/anxiety	Every clinic visit ✓
	α-Gal A enzyme activity and *GLA* mutation analysis	If not previously determined
Renal	Glomerular filtration rate (measured GFR [preferred] or estimated [eGFR] using appropriate formulae)	Annually if low risk, every 6 months if moderate risk, and every 3 months if high to very high risk;[a] measured GFR only once yearly because of complexity
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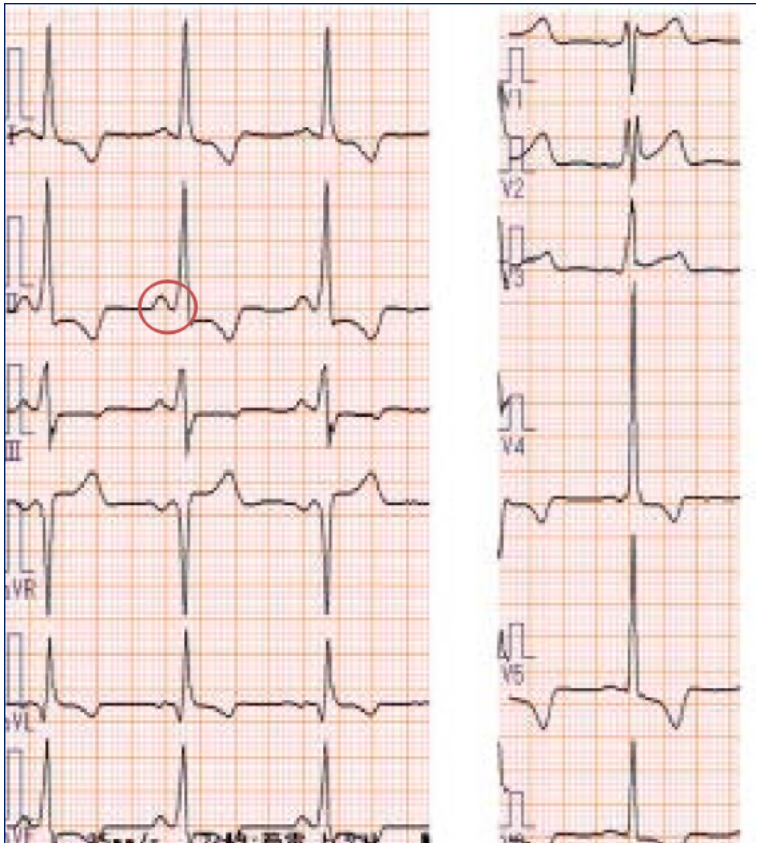
Skeletal	Bone dual-energy X-ray absorptiometry (DEXA)	Consider
Ophthalmological	Ophthalmological screening	Ophthalmological screening as clinically indicated

Annuel _____ Points particuliers _____ ✓ clinique

Holter ECG longue durée

Anomalies : 50% des patients



- 16 patients (12 hommes)
- Cardiomyopathie avancée (HVG + fibrose)
- Holter ECG 24 heures normal
- Reveal - suivi 1,2 (0,3-2) ans
- 21 évènements détectés (15 amenant à modification PEC cz 8 (50%) patients (PM,DAI,AVK)
  - 4 pauses > 3 sec
  - 7 bradycardie
  - 5 FA > 3 min
  - 5 TV (3 TVS, 2 TVNS)

Usefulness of an Implantable Loop Recorder to Detect Clinically Relevant Arrhythmias in Patients With Advanced Fabry Cardiomyopathy

Frank Weidemann, MD[a,b,*], Sebastian K.G. Maier, MD[b,c], Stefan Störk, MD[b], Thomas Brunner[b], Dan Liu, MD[b], Kai Hu, MD[b], Nora Seydelmann, MD[b], Andreas Schneider, MD[b], Jan Becher, MD[b,c], Sima Canan-Kühl, MD[d], Daniela Blaschke, MD[d], Bart Bijnens, PhD[e], Georg Ertl, MD[b], Christoph Wanner, MD[b], and Peter Nordbeck, MD[b]

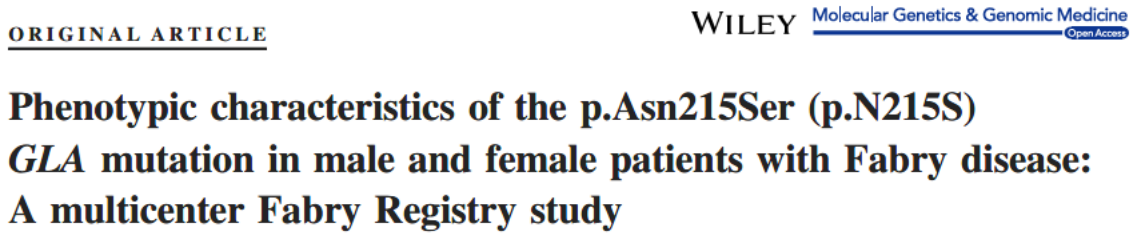
Am J Cardiol 2016

LE COEUR

Variant cardiaque de maladie de Fabry

- **Formes « late onset »,**
  - activité enzymatique résiduelle αGal 2-20% N,
  - absence de signes précoces classiques de MF (douleurs neuropathiques, atteinte GI, angiokératomes, cornée verticillée),
  - Manifestations cardiaques (HVG, troubles conductions, arythmie)
  - Mutation faux sens p.N215S,
- Comparaison au sein du Fabry registry
  - variants cardiaques, 125 patients (66 F, 59 H)

    vs
  - formes « classiques », 401 patients (237 F, 164 H)

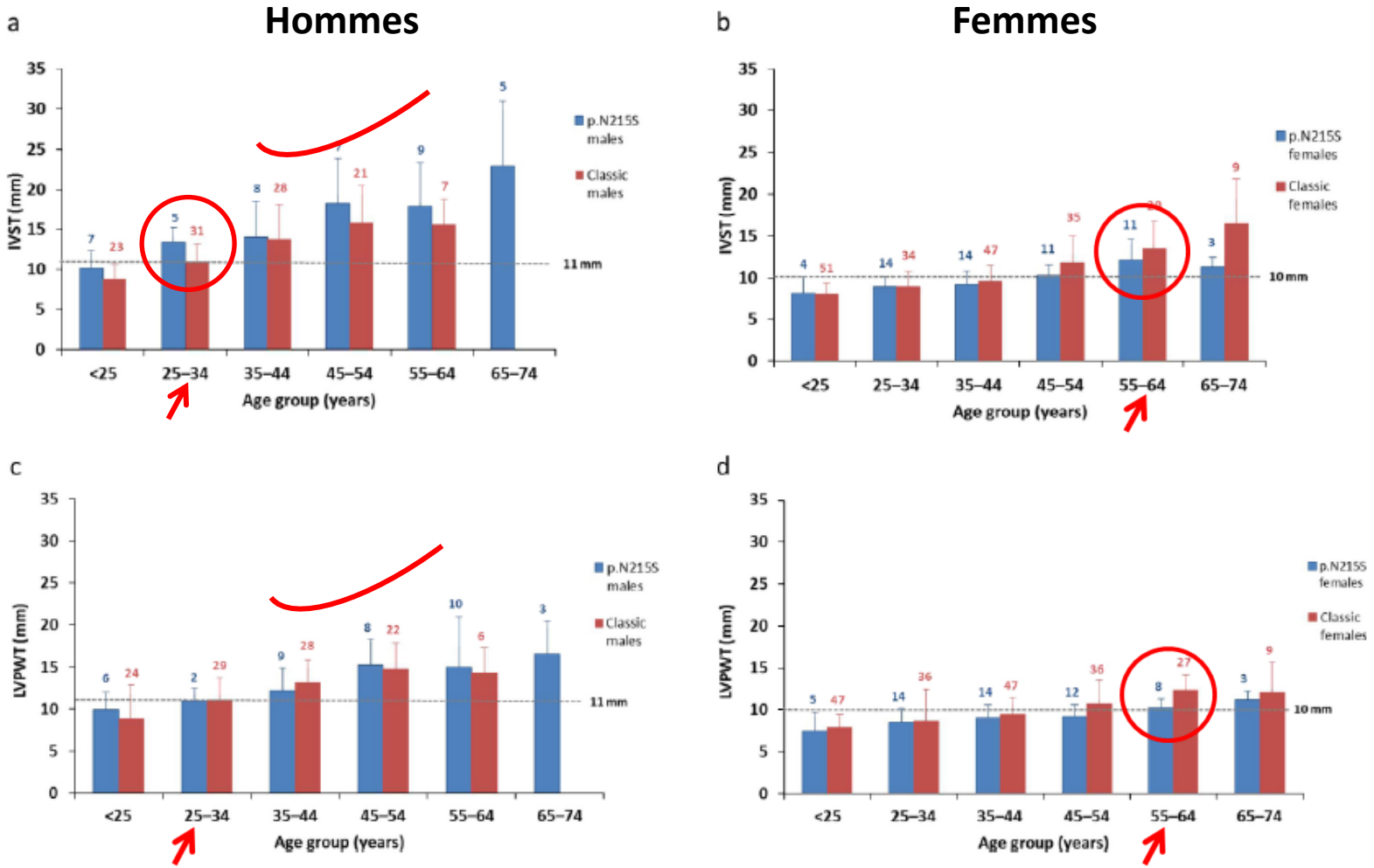

ORIGINAL ARTICLE

WILEY Molecular Genetics & Genomic Medicine Open Access

Phenotypic characteristics of the p.Asn215Ser (p.N215S) *GLA* mutation in male and female patients with Fabry disease: A multicenter Fabry Registry study

Variant cardiaque *vs* forme classique

septum inter-ventriculaire et paroi postérieure



Variant cardiaque *vs* forme classique

évènements cliniques sévères

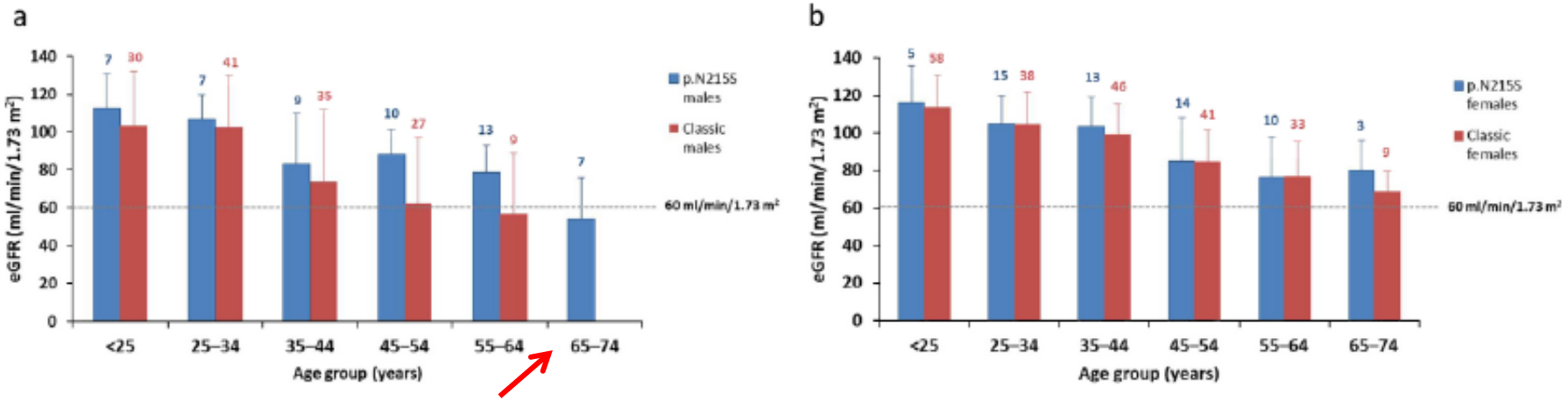
Severe clinical events	p.N215S males (*n* = 59)		Classic males (*n* = 164)		p.N215S females (*n* = 66)		Classic females (*n* = 237)	
	n (%)	Mean age (*SD*), years	*n* (%)	Mean age (*SD*), years	*n* (%)	Mean age (*SD*), years	*n* (%)	Mean age (*SD*), years
Any event	19 (32)	52.4 (11.8)	54 (33)	38.3 (10.9)	6 (9)	50.2 (11.6)	47 (20)	49.2 (13.6)
Cardiac event	18 (31)	52.3 (12.1)	34 (21)	43.3 (10.6)	5 (8)	51.1 (12.8)	36 (15)	50.2 (13.6)
Angina pectoris	-	-	9 (5)	-	3 (5)	-	14 (6)	-
Arrhythmia	10 (17)	-	13 (8)	-	1 (2)	-	14 (6)	-
Congestive heart failure	1 (2)	-	4 (2)	-	-	-	-	-
Myocardial infarction	1 (2)	-	2 (1)	-	-	-	-	-
Significant cardiac procedure	6 (10)	-	6 (4)	-	1 (2)	-	8 (3)	-
Renal event	-	-	25 (15)	36.9 (11.3)	1 (2)	45.0	1 (<1)	41.0
Chronic dialysis	-	-	23 (14)	-	-	-	-	-
Transplant	-	-	2 (1)	-	1 (2)	-	1 (<1)	-
Cerebrovascular event	1 (2)	54.1	12 (7)	34.8 (8.8)	-	-	15 (6)	47.2 (13.7)
Hemorrhagic stroke	-	-	2 (1)	-	-	-	-	-
Ischemic stroke	1 (2)	-	10 (6)	-	-	-	15 (6)	-
Death	-	-	2 (1)	47.0 (7.7)	-	-	1 (<1)	66

SD, standard deviation.

Principalement cardiologiques

Variant cardiaque *vs* forme classique

quelle évolution pour la fonction rénale ?



- Une dégradation de la fonction rénale chez 17% des hommes p.N215S
- Principalement après 65 ans ↗
- Rare chez les femmes (3%)

Le variant cardiaque au final…

- **p.N215S** : mutation à l'origine d'une authentique MF
- **Manifestations cliniques graves** :
  - principalement **cardiaques** jusqu'à la **fin de l'âge adulte**
  - Atteinte cardiaque semble être **progressive** en particulier chez les hommes
  - **Peut devenir aussi grave** (ou parfois plus grave) que dans les formes classiques
- Insuffisance rénale :
  - observée chez qq hommes p.N215S plus tard dans la vie, rare chez les femmes
- **Diagnostic précoce** et **surveillance étroite** de l'état cardiaque nécessaires
  - **Traitement spécifique** de la MF
  - **Traitement des facteurs de risque CV**
  - **Dépistage familial** pour un diagnostic précoce

Un screening « cardiologique » en cas de CMH

ORIGINAL ARTICLE

Journal of Human Genetics (2016), 1–6

www.nature.com/jhg

Fabry disease in patients with hypertrophic cardiomyopathy: a practical approach to diagnosis

Jiwon Seo[1,4], Minji Kim[1,4], Geu-Ru Hong[1], Dae-Seong Kim[2], Jang-Won Son[3], In Jeong Cho[1], Chi Young Shim[1], Hyuk-Jae Chang[1], Jong-Won Ha[1] and Namsik Chung[1]

273 patients consécutifs
3 patients FD diagnostiqués (prévalence 4,6%; 2 femmes et 1 homme)
Avec au moins 3 critères, prévalence 18,8%

Vers un screening « cardiologique »

Les critères de dépistage

1. **CMH « atypique »**
2. **Présence ou ATCD documenté** de
   - **Arythmie** (tachycardie atriale, fibrillation atriale, tachycardie ventriculaire)
   - **ESV symptomatiques**
   - **Bloc AV de haut degré**
3. **Intervalle PR court** (< 120 ms)
4. **Symptômes de dysautonomie** :
   - Syncope inexpliquée
   - Hypotension orthostatique
   - Vertiges récurrents
   - Incompétence chronotrope

Seo et al. *Journal of Human Genetics* 2016

MUSCLE/HYPER CKEMIE

Maladie de Pompe

Incidence : 1/100 000 à 200 000 naissances

Mode de transmission :

- Transmission sur un mode récessif autosomal affectant les garçons et les filles

- Anomalies génétiques du gène qui régule la synthèse de l'**Alpha-1,4-glucosidase** acide (maltase acide) situé en 17q23

Diagnostic biologique

Mesure de l'activité enzymatique de l'Alpha-1,4-glucosidase (**maltase acide**) dans les lymphocytes et fibroblastes

Forme infantile

- -Hypotonie majeure, Difficultés de succion et déglutition
- -Cardiomyopathie hypertrophique
- -Hépatomégalie
- -Espérance de vie limitée en l'absence d'ERT (avant 2 ans)

Formes juvénile et adulte

- -**Myopathie des ceintures** débutant aux membres inférieurs
- -Évolution variable
- -Espérance de vie plus ou moins limitée (muscles respiratoires)

Une présentation clinique hétérogène avec des signes non spécifiques

Atteintes neuro-vasculaires

Cas de dolichoectasie et anévrisme du tronc basilaire (AVC, AIT)

Atteintes cardiaques

Rares cas chez les adultes

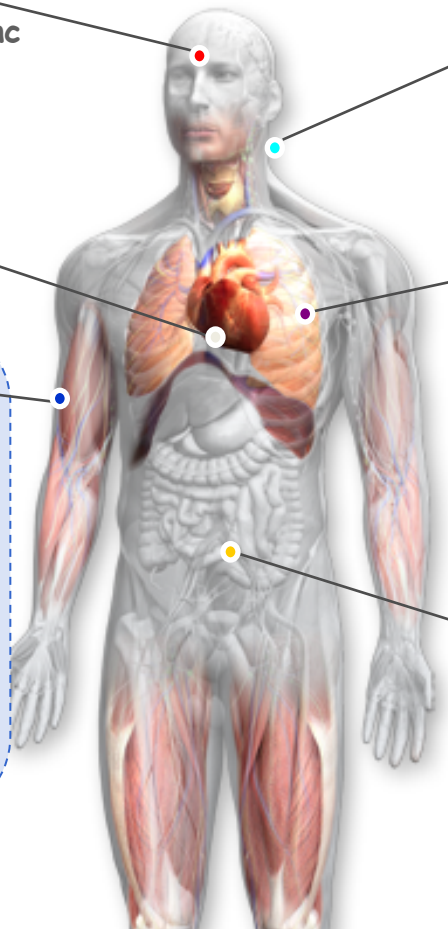
Atteintes musculo-squelettiques

Faiblesse de la ceinture scapulaire
➔ décollement des omoplates

Faiblesse des muscles axiaux
➔ déformations du rachis (scoliose, lordose, cyphose)

Faiblesse de la ceinture pelvienne

➔douleurs et asthénie, difficultés à monter les escaliers, chutes fréquentes



Difficultés à l'alimentation

Difficultés à mâcher et à avaler

Atteintes respiratoires

Faiblesse des muscles respiratoires

➔ Insuffisance respiratoire restrictive

➔ Infections respiratoires fréquentes

Atteintes hépato-gastro-intestinales

Diarrhées, reflux gastro-œsophagien

Bilan hépatique perturbé

↑ CK, ↑ transaminases, ↑ LDH

Difficultés à poser le diagnostic de maladie de Pompe

Available online at www.sciencedirect.com
ScienceDirect
Neuromuscular Disorders 28 (2018) 586–591
www.elsevier.com/locate/nmd

Targeted gene panel screening is an effective tool to identify undiagnosed late onset Pompe disease

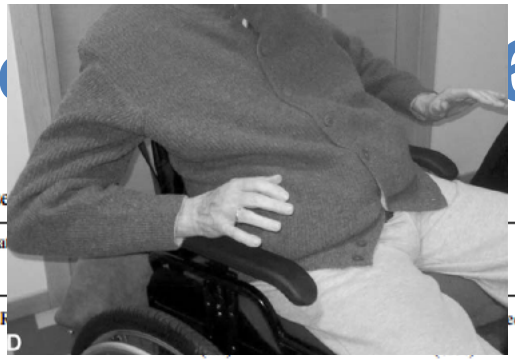
Marco Savarese[a,b], Annalaura Torella[b,c], Olimpia Musumeci[d], Corrado Angelini[e], Guja Astrea[f], Luca Bello[g], Claudio Bruno[h], Giacomo Pietro Comi [i], Giuseppina Di Fruscio[b], Giulio Piluso[b], Giuseppe Di Iorio[j], Manuela Ergoli[k], Gaia Esposito[b], Marina Fanin[g], Olimpia Farina[j], Chiara Fiorillo[h], Arcomaria Garofalo[b], Teresa Giugliano[b], Francesca Magri[i], Carlo Minetti[h], Maurizio Moggio[l], Luigia Passamano[k], Elena Pegoraro[g], Ester Picillo[k], Simone Sampaolo[j], Filippo Maria Santorelli[f], Claudio Semplicini[g], Bjarne Udd[a,m], Antonio Toscano[d], Luisa Politano[k,*], Vincenzo Nigro[b,c]

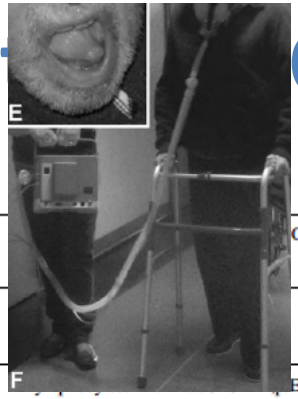
Réseau association italienne de Myologie, Panel de gènes myopathies : MotorPlex
504 patients sans diagnostic identifiés,
275 (259 familles) phénotypes atteinte des **ceintures et/ou hyperCKémie** : groupe à haut risque de LOPD

Maladie de Pompe tardive (LOPD) identifiée chez **10 patients à haut risque** (9 familles)
7 autres parents affectés identifiés par analyse de ségrégation
Prévalence de LOPD : **3,63%** (10/275)
Facteurs pouvant entraver le diagnostic de LOPD

- Biopsie prise à défaut > ½
- Patients perdus de vue (détection précoce des signes respiratoires)
- Atypies cliniques (dysphagie, pseudohypertrophie, hypertrophie mollets)
- Difficultés interprétation génétique (patient 1, LGMD2A, *CAPN3*)

Phén 6 pa OPD





Patients with late-onset pompe dise

Case	Onset	Age at diagnosis (y)	Symptoms a									G_009822.1 or NM_000152.3)
			Limb weak.	R				ed ml	Histology			2nd allele
I	early adul.	49	prox.	no	fatigability	n.a.	5–10×	n.a.	myopathic		E262K [23]	c.-32-13T >G [18]
II*	adul.	71	prox.	no	myalgia	40	5–10×	850 (22%)	myopathic	DBS: 0	c.1564C >G;p.P522A [27]	
III	adul.	63										A;p.G643R
IV,1	early adul.	40										T;p.R375L
IV,2	early adul.	47	prox.	yes		n.a.	2.5–5×	n.a.	n.a.	n.a.		
IV,3	early adul.	50	not observed	no		n.a.	2.5–5×	n.a.	n.a.	n.a.		
IV,4	early adul.	45	prox.	no		n.a.	2.5–5×	n.a.	vacuoles	n.a.		
V,1	adol.	42	prox.	no	fatigability, myalgia	135	5–10×	950 (20%)	vacuoles	DBS: 0.20	c.1124G >T;p.R375L [24]	
V,2	adul.	33	prox.	no	fatigability	566	5–10×	3000 (90%)	n.a.	DBS: 0.20		
V,3	child.	45	prox.	no	n.a.		2.5–5×	n.a.	n.a.	DBS: 0.08		
VI,1	early adul.	63	prox. and axial	yes	fatigability, myalgia	n.a.	normal	1520 (38%)	n.a.	DBS: 0.24	c.2237G >A;p.W746* [26]	
VI,2	adul.	61	prox.	yes	fatigability	418	2.5–5×	2040 (46%)	myopathic	DBS: 0.22		
VI,3	adul.	64	prox.	yes		n.a.	2.5–5×	1550 (48%)	n.a.	DBS: 0.16		
VII	adol.	33	prox. and dist.	no	cramps	n.a.	2.5–5×	5260 (112%)	vacuoles	DBS: 0.20	c.784G >A;p.E262K [23]	
VIII	early adul.	56	prox.	no	fatigability, myalgia	385	2.5–5×	2480 (75%)	myopathic	DBS: 0.13	c.G989A;p.W330* [27]	
IX	early adul.	n.a.	prox.	yes	fatigability, cardiac involvement	WCB	n.a.	n.a.	n.a.	n.a.	c.1124G >T;p.R375L [24]	

y = years; Resp. = respiratory; 6MWT = 6 minutes walking test; N = normal; adult. = adulthood; child. = childhood; adol. = adolescence; prox. = proximal; dist. = distal; n.a. = not available; DBS = dried blood spot; CK = creatine kinase; FVC = forced vital capacity; WCB = Wheel-chair-bound.

NEXT GENERATION SEQUENCING DETECTION OF LATE ONSET POMPE DISEASE

Muscle Nerve 2016

CORRADO ANGELINI, MD,[1] MARCO SAVARESE, PhD,[2,3] MARINA FANIN, PhD,[4] and VINCENZO NIGRO, MD, PhD[2,3]

Age moyen **50,8 ± 11,7 ans** [33-71]

Délai moyen du diagnostic **21,5 ans** [11-38]

The genetic basis of undiagnosed muscular dystrophies and myopathies

Results from 504 patients

Neurology® 2016;87:71-76

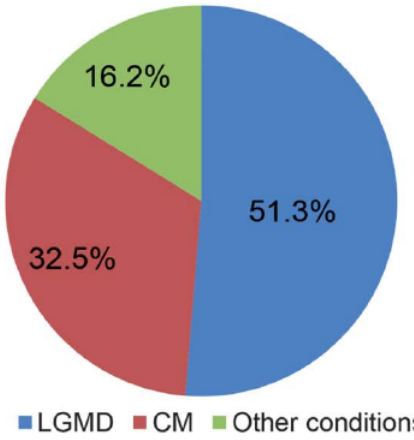
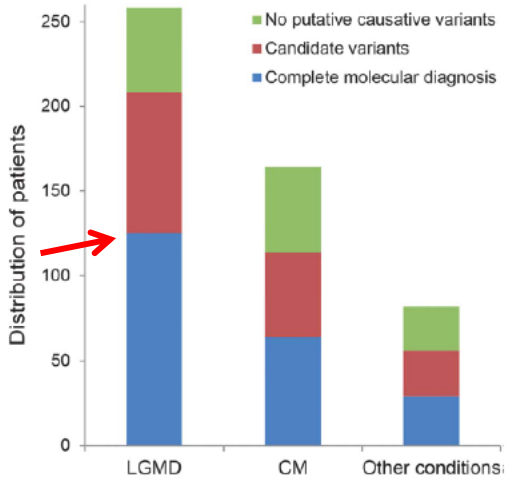


Figure 3 Distribution of the 504 patients tested according to clinical phenotype and molecular findings



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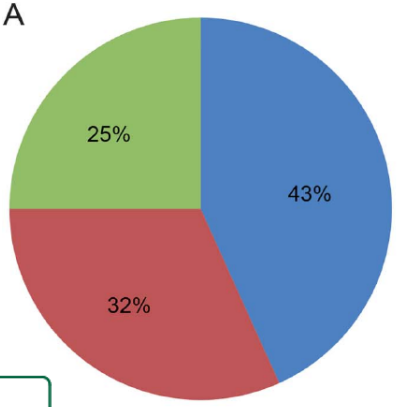


Table 1 LGMD genes[22]

Disease	Locus	Gene	No. of patients
LGMD1B	1q22	*LMNA*	3
LGMD1C	3p25.3	*CAV3*	2
LGMD2A	15q15	*CAPN3*	22
LGMD2B	2p13.2	*DYSF*	15
LGMD2C	13q12	*SGCG*	4
LGMD2D	17q21	*SGCA*	10
LGMD2E	4q12	*SGCB*	6
LGMD2G	17q12	*TCAP*	1
LGMD2H	9q33.1	*TRIM32*	1
LGMD2I	19q13.3	*FKRP*	7
LGMD2J	2q24.3	*TTN*	5
LGMD2K	9q34.1	*POMT1*	1
LGMD2L	11p13	*ANO5*	15
LGMD2M	9q31	*FKTN*	2
LGMD2N	14q24	*POMT2*	6
LGMD2R	2q35	*DES*	1
LGMD2S	4q35.1	*TRAPPC11*	2
LGMD2T	3p21	*GMPPB*	2
LGMD2V	17q25	*GAA*	10

Table 2 Other myopathy genes

Locus	Gene	No. of patients
1q42.13	*ACTA1*	2
1p21	*AGL*	2
21q22.3	*COL6A2*	4
2q37	*COL6A3*	1
11q22.3-q23.1	*CRYAB*	1
Xp21.2	*DMD*	7
19p13.2	*DNM2*	5
Xq28	*EMD*	1
7q32	*FLNC*	4
17q25.2-q25.3	*GLA*	1
3p12	*GNE*	3
3p22.1	*GTDC2*	1
3q24	*GYG1*	1
12q13.2	*ITGA7*	2
6q22-q23	*LAMA2*	8
Xq28	*MTM1*	5
17p13.1	*MYH2*	1
14q12	*MYH7*	8
5q31	*MYOT*	1
2q23.3	*NEB*	9
11q12-q13.2	*PYGM*	3
20p13	*RYR1*	25
1p36.13	*SEPN1*	2
18p11.32	*SMCHD1*	1
6q25	*SYNE1*	1
14q23.2	*SYNE2*	1
9p13	*TPM2*	1
1q21.2	*TPM3*	2

NGS : un spectre élargi des phénotypes cliniques associées aux myopathies métaboliques

Broadening the spectrum of clinical phenotypes associated with metabolic myopathies by next generation sequencing.

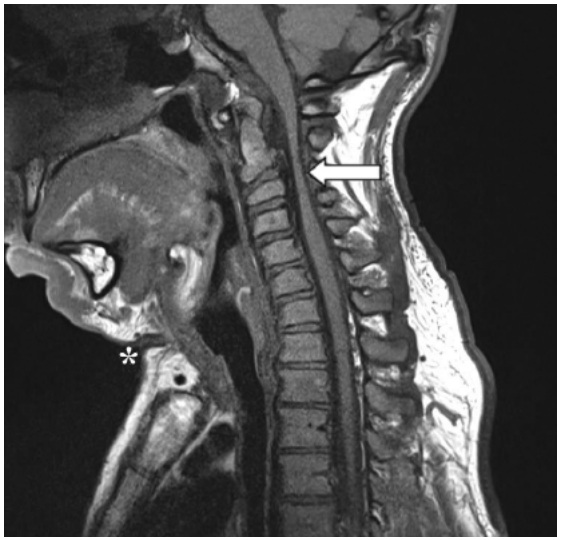
Reference	Genetic approach	Cohort	Results	Atypical elements
Ghaoui et al. [32]	WES	LGMD (n = 60)	1 *GAA**	n.a.
			1 *CPT2*	fixed weakness
			1 *PYGM*	fixed weakness
Todd et al. [33]	WES	LGMD (n = 38)	1 *GBE*	fetal akinesia and multiple pterygium syndrome
Lévesque et al. [34]	Targeted resequencing	Muscle Disorders (n = 34)	1 *GAA*	long lasting history of gait disturbances
Kuhn et al. [35]	Targeted resequencing	LGMD (n = 58)	1 *GBE*	minimal non-lysosomal glycogen storage without any evidence of polyglucosan bodies
Reddy et al. [36]	WES	LGMD (n = 55)	1 *GAA*	n.a.
			1 *VCP*	
Johnson et al. [37]	WES	LGMD and/or hyperCKemia (n = 606)	8 *GAA*	n.a.

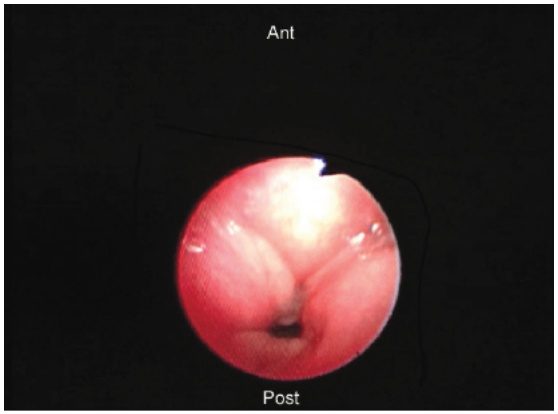
n.a. = not available; WES = whole exome sequencing.
* LOPD patient was identified in a pre-NGS screening.

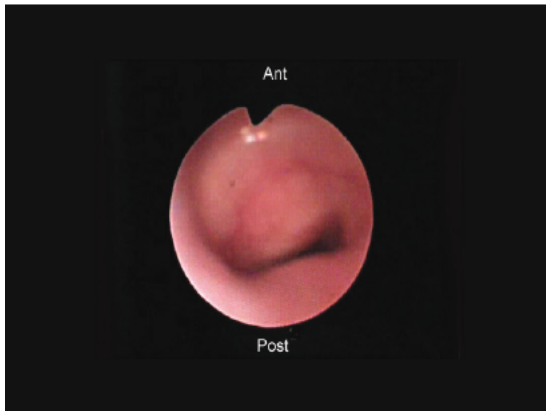
20-30% des myopathiques seraient **porteurs de mutations causales** de myopathies dont le **phénotype est inhabituel**

MUCOPOLYSACCHARIDOSES

MPS et risque anesthésique : un paysage difficile et changeant





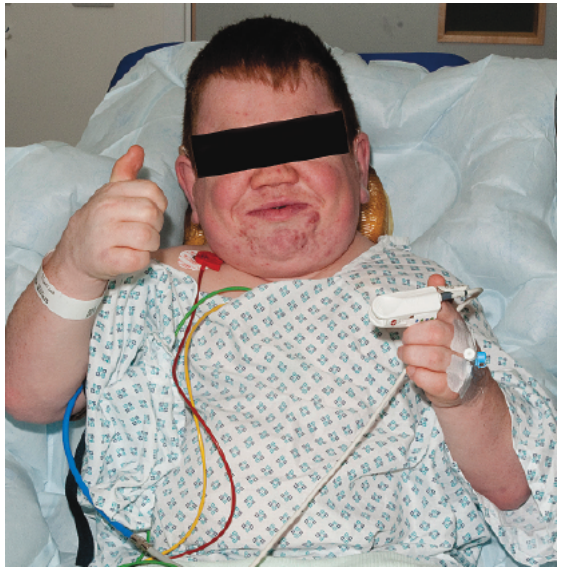


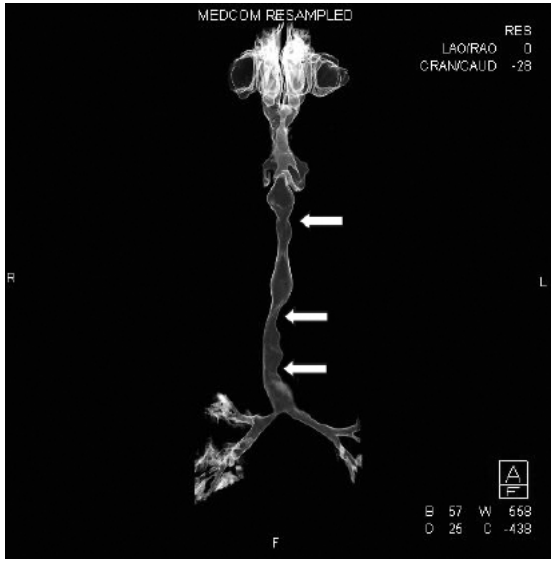
Syndrome Hurler-Scheie femme 25 ans remplacement valve mitrale

Anesthesia Risk and the Mucopolysaccharidoses: A Challenging and Changing Landscape

Robert W. M. Walker[1] James Garbarino[2]

Hurler-Scheie homme 27 ans laminectomie





18 ans (40 kg) Hunter

SPLENOMEGALIE…ENCORE

Kawazoe *et al. BMC Neurology* (2018) 18:117
https://doi.org/10.1186/s12883-018-1124-2

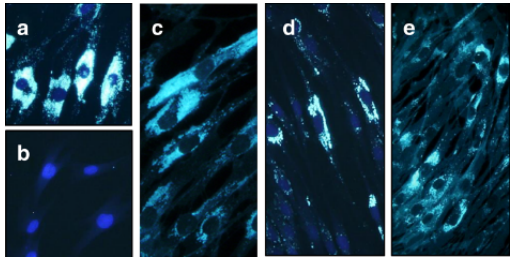
BMC Neurology

CASE REPORT Open Access

Phenotypic variability of Niemann-Pick disease type C including a case with clinically pure schizophrenia: a case report

- **Cas n°1** : Homme 25 ans, 14 années de déficience intellectuelle, maladresse, ataxie spastique, dysphagie, chutes. Paralysie supra nucléaire et mouvements involontaires. Splénomégalie
- **Cas n°2** : JF 28 ans, splénomégalie dans l'enfance, hallucinations auditives, énurésie, paralysie du sommeil (3, 6 et 9 ans). Dystonie orofaciale et mandibulaire (27 ans)
- **Cas n°3** : examinée à 8 ans, RAS. Schizophrénie à 22 ans, splénomégalie échographique

Diagnostic : test à la filipine sur fibroblastes



Messages pour l'interniste et les autres…

- **Gaucher : retard au diagnostic, toujours…**
  - **MGUS/myélome: penser Gaucher**
  - Les **7 signes** d'alerte du Gaucher
  - Traitement oral (TRS) MG une arme supplémentaire efficace et bien tolérée (8 années de recul)
- **Recommandations actualisées maladie de Fabry**
  - **Génotypage** et confrontation génotype-clinique
  - Quand initier une ERT, comment surveiller, quel calendrier ?
  - Comment **dépister les formes cardiologiques** (variants LO) ? Et parler à votre cardiologue… ☺
- **Maladie de Pompe : retard au diagnostic,…**
  - **HyperCKémie et/ou atteinte des ceintures** : penser Pompe (maltase acide, NGS)
  - Intérêt **techniques NGS/WES**
- **Risque anesthésique des MPS**
- Splénomégalie et signes neuro-psychiatrique des adolescents et jeunes adultes : **penser NPC**…