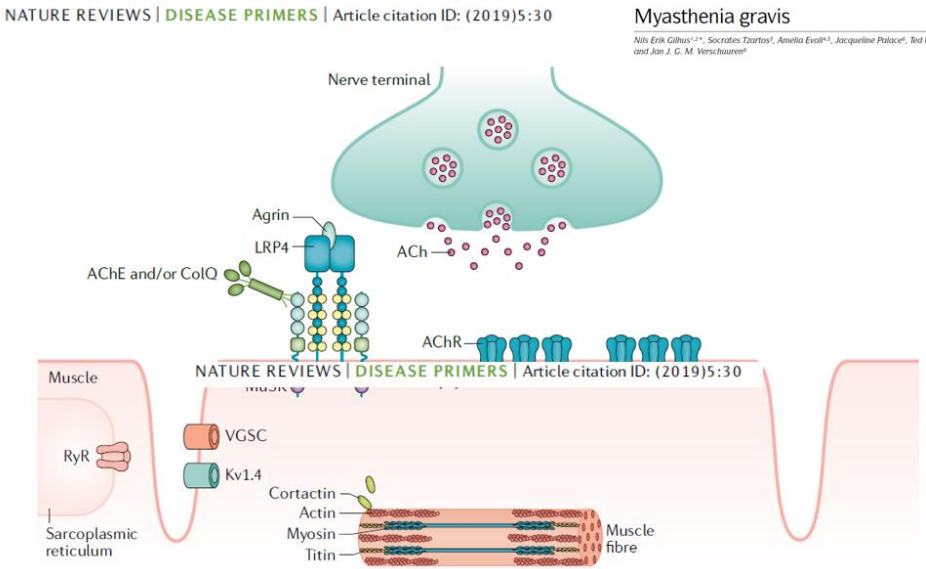
Myasthenie



Diagnostic différentiel

CAUSES	PRE-SYNAPTIQUE	POST-SYNAPTIQUE
AUTOIMMUNE	Sd de Lambert Eaton Ac anti-canaux calciques	Myasthénie Anti-récepteurs AC Anti-MuSK Anti-LRP4
IATROGENE - TOXIQUE	Botulisme	Curare
GENETIQUE	Myasthénies congénitales	Myasthénies congénitales

- Pathologie autoimmune de la jonction neuromusculaire post-synaptique
- Epidemio :
  - Pathologie rare : prévalence 1/10000
  - Sex ratio 2H/3F
  - A tout âge mais pics F 20-30 ans H 50-60 ans
- Diagnostic basé sur la clinique, l'EMG, les autoanticorps
- Evolution par poussées / rémissions rarement complètes ou permanentes sur les formes généralisées

Clinique

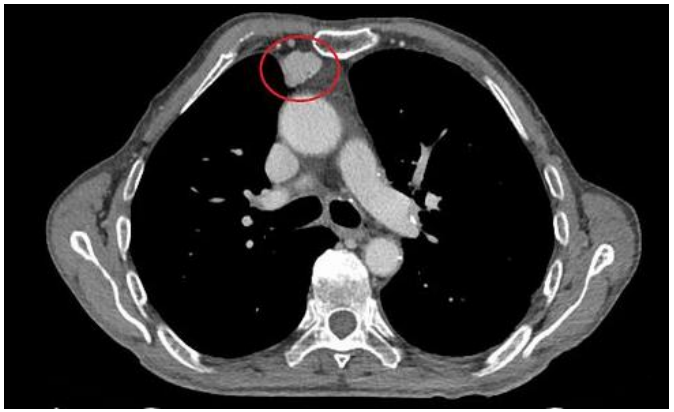
- Faiblesse et fatigabilité musculaire se renforçant à l'effort répété
- Distribution de l'atteinte musculaire évocatrice
  - Muscles de la face fréquente et souvent initiale :
    - ptosis, diplopie (souvent intermittente)
    - expression « sévère »,
    - troubles de la mastication , dysarthrie
    - voix nasonnée, troubles de la déglutition (atteinte bulbaire)
  - Sans traitement, 85% généralisation avec atteinte muscles des membres proximale et parfois asymétrique. ROT conservés

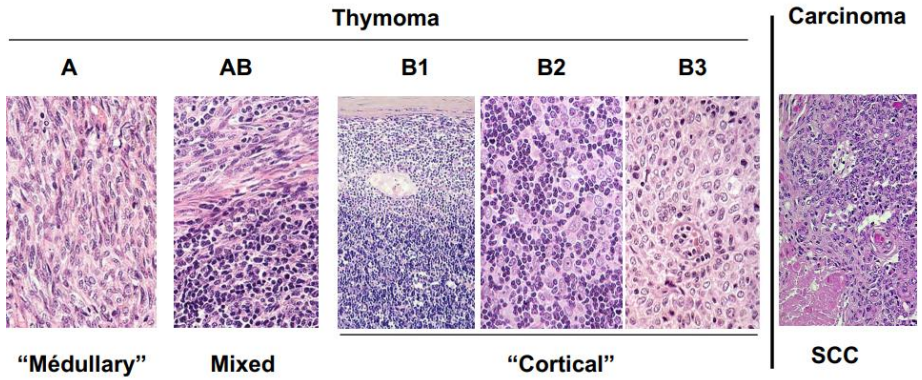
- Test au glaçon
- Pas d'autre signe neurologique

- Facteurs déclenchant : grossesse, infection, instauration d'un nouveau traitement

Recherche de pathologies associées

- Anomalies thymiques dans 75% des cas
  - Hyperplasie thymique
  - Thymome (scanner) : 15% des patients myasthéniques
  - 30% des patients avec thymome développent une Myasthénie
- Hyperthyroïdie
- Autres maladies autoimmunes



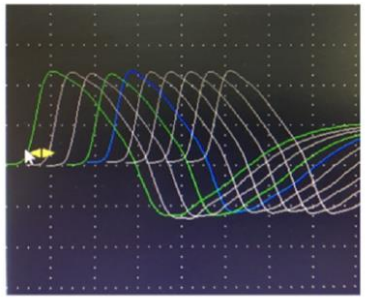


Tests diagnostiques

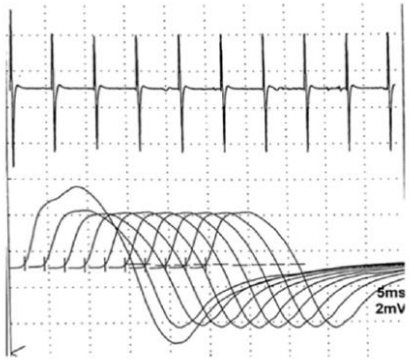
- EMNG
  - Test sur muscles atteints ou proximaux
  - Stimulations à basse fréquence 3 sec et recueil des potentiels évoqués
  - Chez myasthénique : décrément rapide de >10-15% de l'amplitude

- Autoanticorps
  - ARAC (IgG1 et IgG3)
  - Anti-MuSK (IgG4)
  - Autres : anti-titin, anti-LPR4, etc…

- Test aux anti-cholinesthérase (Prostigmine, Tensilon, ..) en hospitalisation ou mise sous traitement d'épreuve



Normal Trapezoid muscle response
No blocks at slow rate (3 Hz)



Decrement in Trapezoid muscle, due to blocking in many muscle fibers

Parésie, déficit de l'élévation, ptosis

Correction après injection de Tensilon

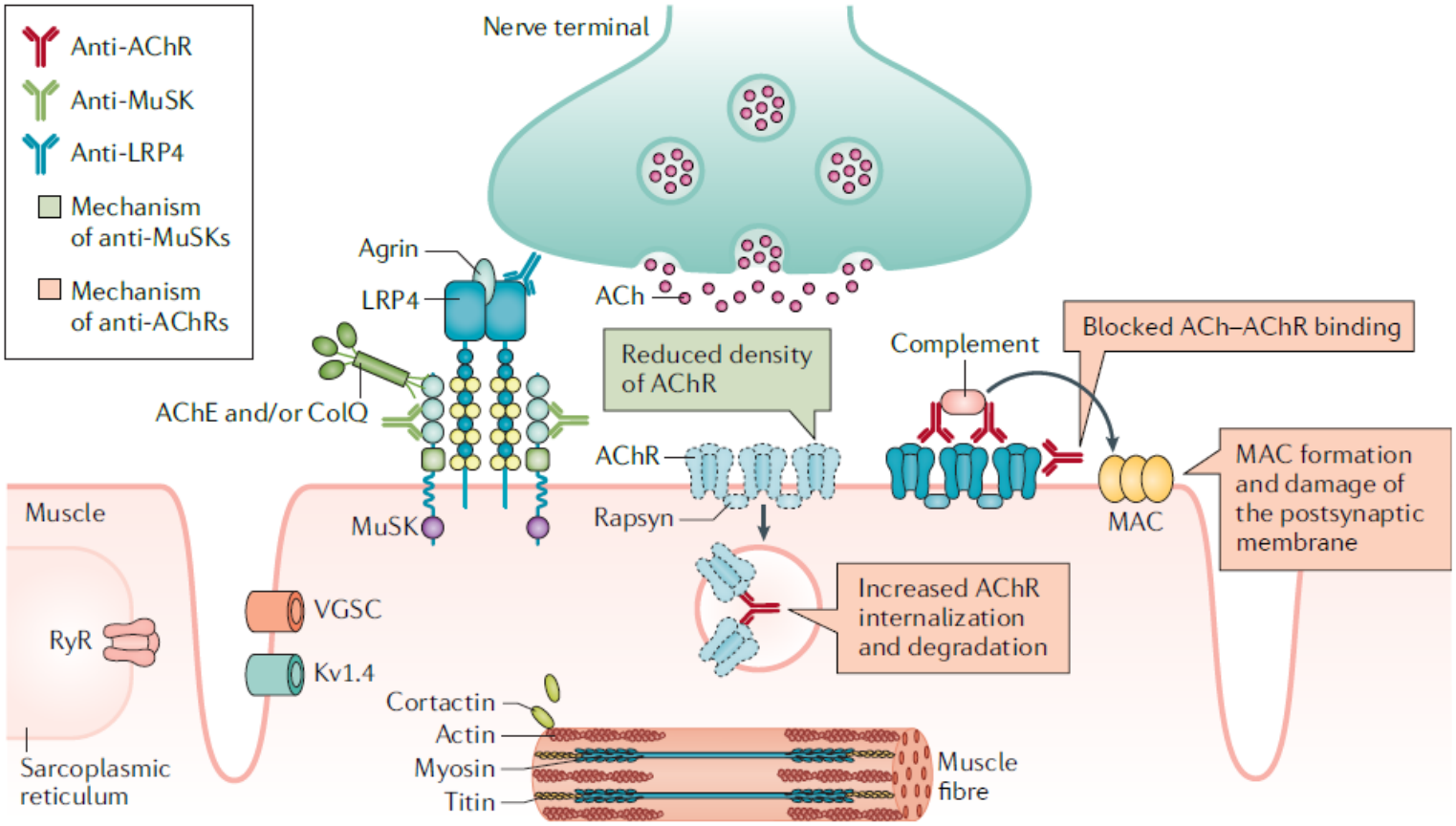


Fig. 3 | **Pathophysiology of MG at the neuromuscular junction.** Anti-acetylcholine (ACh) receptor (AChR) antibodies activate complement, leading to damage of the postsynaptic membrane at the neuromuscular junction through production of the membrane attack complex (MAC). Anti-AChR antibodies can also crosslink AChRs, leading to their accelerated internalization and degradation rate. Some antibodies can directly block the ACh binding site. Anti-muscle-specific kinase (MuSK) antibodies do not activate complement and typically prevent the interaction of MuSK and lipoprotein-receptor-related protein 4 (LRP4), among other proteins, leading to reduced AChR clustering on the postsynaptic membrane. The pathogenicity of anti-LRP4 antibodies in myasthenia gravis (MG) remains to be established. Additional antibodies, such as anti-collagen Q (ColQ), anti-titin, anti-ryanodine receptor (RyR), anti-cortactin and anti-voltage-gated potassium channel (Kv1.4) have been demonstrated in patients with MG, although any pathogenetic significance remains unknown. AChE, acetylcholinesterase; VGSC, voltage-gated sodium channel.

Curr Opin Neurol. 2018 Oct;31(5):517-525.

Table 1. Acetylcholine receptor-myasthenia gravis, muscle-specific kinase-myasthenia gravis, and lipoprotein receptor-related protein 4-myasthenia gravis subgroups and related clinical features

Myasthenia gravis subgroups	Age at onset (years)	Sex	Thymic histology	Additional autoantibodies	Clinical presentation
AChR-MG					
Early-onset	<50	F > M	Hyperplasia	Rare	Ocular frequently converting in generalized
Late-onset	>50	M > F	Atrophy	Common (anti-titin, anti-RyR)	Generalized
Thymoma-associated	Any, but more frequently >50	M > F	Thymoma	Common (anti-titin, anti-RyR, anti-actin, and other muscle proteins)	Generalized, severe disease
MuSK-MG	Usually <50	F > M	Normal (hyperplasia in 23% of patients with MuSK-CBA Abs [5])	Rare	Generalized, severe disease
LRP4-MG	Any	F > M	Normal (hyperplasia in 31% of single positive patients and 67% of double LRP4/AChR-positive patients [9]; absence of thymoma	Rare (anti-AChR or anti-MuSK)	Ocular or generalized, mild symptoms; severe symptoms at onset in double LRP4/AChR-positive or LRP4/MuSK-positive patients [9]

AChR, acetylcholine receptor; CBA, cell-based assay; F, female; LRP4, lipoprotein receptor-related protein 4; M, male; MuSK, muscle-specific kinase; RyR, ryanodine receptor.

Table 1 | **Classification of MG subgroups**

Subgroup	Autoantibody	Age at onset	Thymus abnormalities
Early-onset MG[a]	AChR	<50 years of age	Hyperplasia common
Late-onset MG	AChR	>50 years of age	Atrophy common
Thymoma MG	AChR	Any	Type AB and B thymoma
MuSK MG	MuSK	Any	Normal
LRP4 MG	LRP4	Any	Normal
Seronegative MG	None detected	Any	Variable
Ocular MG[b]	AChR, MuSK, LRP4 or none	Any	Variable

Myasthenia gravis

Nils Erik Gilhus[1,2], Socrates Tzartos[3], Amelia Evoli[4,5], Jacqueline Palace[6], Ted M. Burns[7] and Jan J. G. M. Verschuuren[8]*

Formes en fonction de l'autoAc

Table 1 Subgroup characteristics of myasthenia gravis-related autoantibodies.

Autoantibody	IgG subclass	Pathogenic mechanism	% of MG patients	Sex ratio (M:F)	Symptoms and severity grade	Thymic change	Detection of pregnant women with MG	Association with neonatal MG
AChR	IgG1, IgG3	Blocking Ach-AChR binding Complement activation AChR cross-linking	85	1:2	Ocular and generalized forms All severity forms	Hyperplasia, thymoma	Common	Common
MuSK	IgG4	Blocking MuSK-LRP4 interaction	5	1:3	Bulbar and respiratory symptoms Mainly severe form	Variable (normal, hyperplasia), no thymoma	Rare	Rare
LRP4	IgG1, (IgG2)	Blocking agrin-LRP4 interaction (complement activation)	2	1:2.5	Ocular and generalized forms Mainly mild form	Variable (normal, hyperplasia, atrophy), no thymoma	Not reported	Not reported

AChR, acetylcholine receptor; F, female; IgG, immunoglobulin G; LRP4, low-density lipoprotein receptor-related protein 4; M, male; MG, myasthenia gravis; MuSK, muscle-specific tyrosine kinase.

TABLE 1 | Summary of autoantibody prevalence, usual detection method and major clinical associations where known*.

Autoantigen	Detection method	% of MG patients	% of dSN-MG patients	Other diseases	Clinical associations	Representative references
AChR	RIPA	80–85%	N.A.	Rare	Thymic abnormalities, thymoma	Several references, reviewed in Gilhus et al. (6)
Clustered AChR	CBA	N.T.	~20% (4–60%)	N.T.	Milder symptoms than AChR+ MG, thymic abnormalities	(40, 45)
MuSK	RIPA	~6% (2–3% in Japanese)	N.A.	Rare	Bulbar symptoms common, no thymic abnormalities	(53, 56, 60)
MuSK	CBA	N.T.	13%	5%	Milder symptoms	(44)
LRP4	CBA	~2%	~19%	3.6% (10–23% in ALS)	Milder symptoms than AChR+ MG, no thymoma	(80) (83)
Titin	ELISA	20–30% (90% in thymoma EOMG	0–3%)	Some	Correlation with thymoma in AChR+ EOMG	(86, 90, 94, 128)
Titin	RIPA	~41%	13.4%	0–3.6%	No correlation with thymoma	(99)
RyR	ELISA	~ 14% in LOMG (75% in thymoma MG)	N.T.	N.T.	Correlation with thymoma in AChR+ MG	(95, 103, 104)
Agrin	ELISA/CBA	2–15%	0–50%	13.8% in ALS	Mild to severe symptoms, moderate response to treatment	(83, 106)
Kv1.4	IP and SDS-PAGE	10–20%	0%	0%	Japanese: Severe symptoms, myasthenic crises, thymoma, cardiac involvement Caucasian: Mild symptoms in LOMG	(110, 112, 113)
Rapsyn	Immunoblots	11%	17%	10% OND 78% SLE	Not known associations	(115, 116)
Cortactin	ELISA, WB	5–10%	~20%	12.5%	Not known associations	(117, 118)
ColQ	CBA	3%	3.4%	5%	Not known associations	(125)

Some studies on potential antigens with small cohort sizes and non-MG-specific findings are not included in the table.
N.T., not tested or not extensively tested; N.A., not applicable; SLE, systemic lupus erythematosus.

Autoantibody Specificities in Myasthenia Gravis; Implications for Improved Diagnostics and Therapeutics

Frontiers in Immunology
February 2020 | Volume 11 | Article 212

Konstantinos Lazaridis[1] and Socrates J. Tzartos[2,3]*

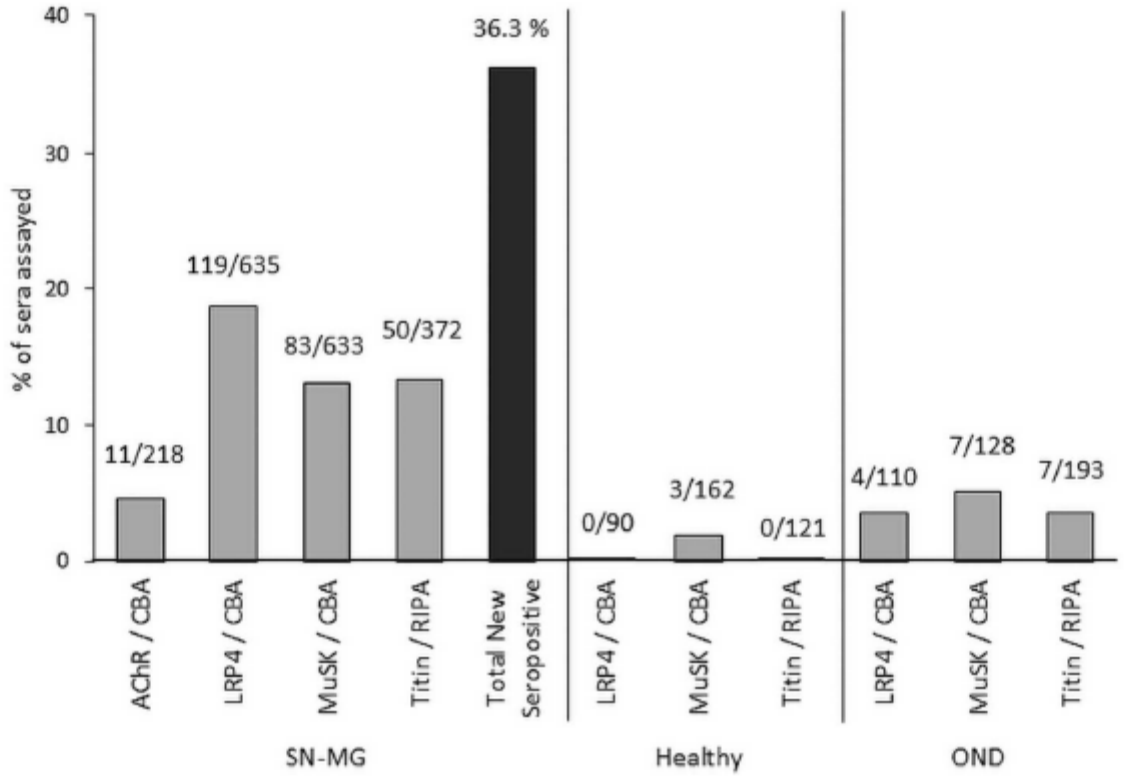


FIGURE 2 | Detection of autoantibodies in SNMG by novel assays. We have used CBA and RIPA for screening a large number of MG patients without detectable autoantibodies by the classical assays, as well as several control samples from healthy individuals or patients with other neuroimmune diseases (OND), from 10 to 13 different European countries (44, 80, 99). The numbers above the bars indicate the number of positive samples and the total tested with each assay. The cumulative percentage (black bar) of new positives among the SNMG samples that were positive in more than one assays were taken into account, so as to avoid overestimation of the total new seropositive patients.

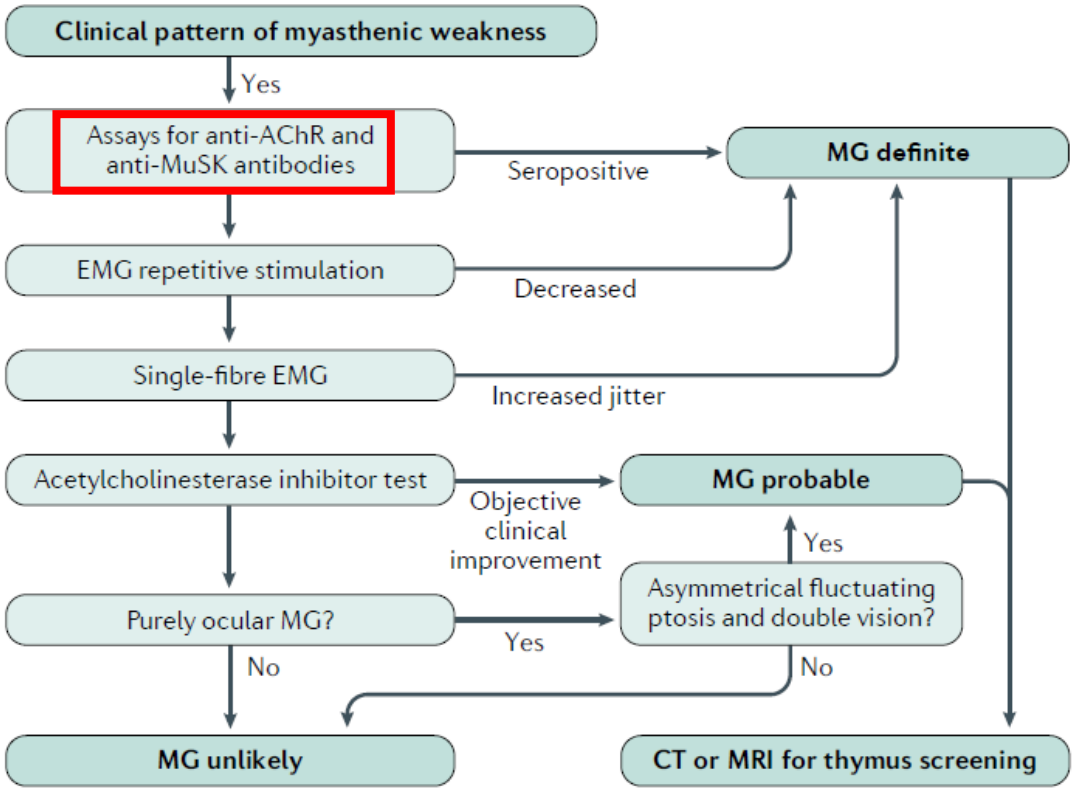


Fig. 5 | **A simplified diagnostic algorithm for MG.** Evaluation of clinical symptoms and signs, antibody testing, neurophysiology, thymus imaging and response to therapy are key elements in the diagnostic work-up of individuals with suspected myasthenia gravis (MG). AChR, acetylcholine receptor; EMG, electromyography; MuSK, muscle-specific kinase.

MuSK

- Muscle Spécific Kinase
- Protéine transmembranaire
  - clustering de l'AC
  - maintenance de la membrane post-synaptique
- Activation par phosphorylation (agrin-LPR4)

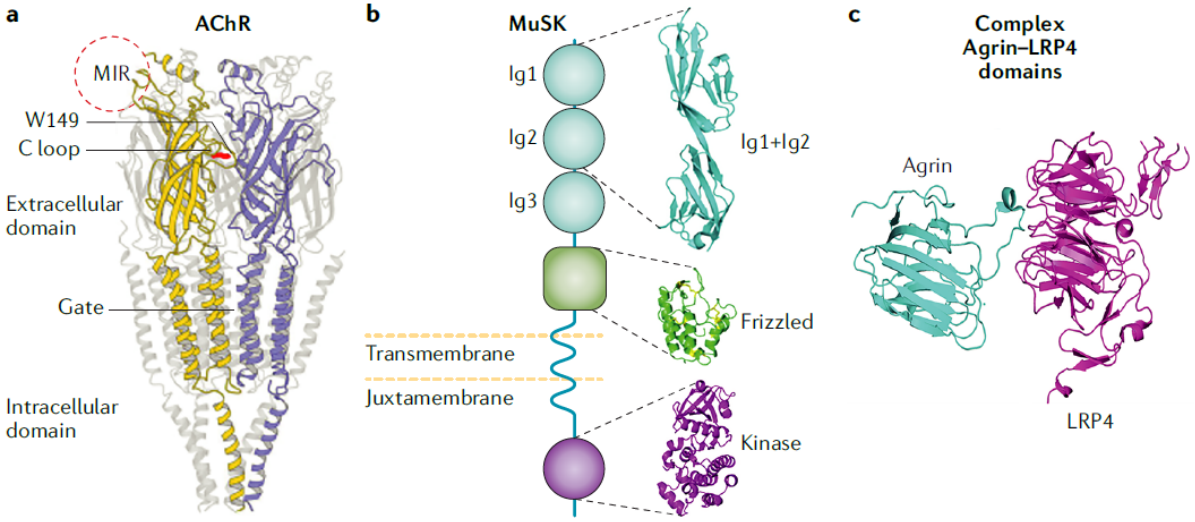


Fig. 2 | **Structures of the main autoantigens in MG. a** | The structure of the Torpedo (a fish, the Pacific electric ray) acetylcholine receptor (AChR), the only available structure of the intact muscle-type AChR, is shown[205]; the site of one of the two main immunogenic regions (MIRs) is marked on the top left. **b** | A schematic drawing of muscle-specific kinase (MuSK) is shown on the left, with domains of known structures that interact with other key proteins on the right[206]. **c** | Lipoprotein-receptor-related protein 4 (LRP4)–agrin complex domains. LRP4 binds to the extracellular matrix proteoglycan agrin[207], triggering MuSK activation and the signalling cascade leading to AChR clustering and postsynaptic differentiation. Ig, immunoglobulin; MG, myasthenia gravis. Part **a** adapted with permission from Unwin, N. Nicotinic acetylcholine receptor and the structural basis of neuromuscular transmission: insights from Torpedo postsynaptic membranes. *Q. Rev. Biophys.* **46**(4), 283–322 (2013). Part **b** adapted from REF.[54], Springer Nature Limited, and with permission from REF.[206], Elsevier. Part **c** adapted from REF.[54], Springer Nature Limited, and with permission from Zong, Y. N. et al. Structural basis of agrin LRP4 MuSK signaling. *Genes Dev.* **26**, 247–258 (2012). © Cold Spring Harbor Laboratory Press.

Process de clustering de l'AC implique la rapsyn qui crée un pont entre l'AC et le cytosquelette

Ac anti-MuSK

- Prévalence
  - 1-10% des patients
  - 40% des Myasthénie ARAC négatives
  - Variations selon les pays (association avec HLA HLA-DRB1∗14, -DRB1∗16 and -DQB1∗05)
- IgG4 +++
- Ac masquent les sites de liaison de la protéine à LRP4 et au collagène Q et diminuent la clustérisation des récepteurs à l'AC
- Liaison aux sites Ig-like de MuSK essentiellement
- Le taux des Ac anti-MuSK est relié à l'activité de la maladie
- Double positivité Ac anti-récepteur de l'AC et anti-MuSK exceptionnelle avec tests traditionnels
- Méthodes de dosage :
  - RIPA avec
  - ELISA
  - FIPA
  - CBA

Myasthénie à anti-MuSK

- Prévalence : pays méditerranéens > nord Europe > Chine

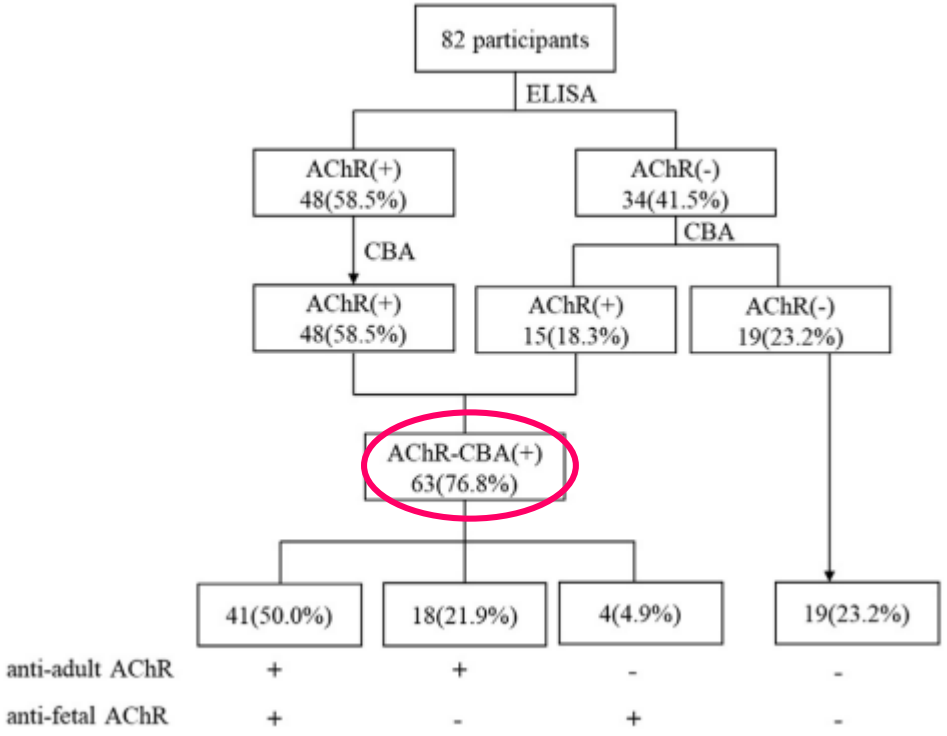
- Typiquement, forme sévère de myasthénie
  - Atteinte bulbaire, respiratoire et muscles du cou
  - Evolution rapide vers un maladie généralisée avec risque vital
  - Atteinte oculaire souvent peu développée avec limitation des mouvements oculaires conjugués fréquente
  - Atteinte limitée des muscles distaux
- 50% de non réponse aux anti-cholinesthérasiques
- EMG : souvent pas de décrémentation au niveau muscles distaux. Meilleur site : muscle orbiculaire

- Réponse au traitements :
  - Corticoïdes à hautes doses + souvent immunosuppresseur (Rituximab +++ actuellement)
  - Echanges plasmatiques plutôt que IgIV

- Evolution identique à Myasthénie classique sans thymome
- Mais parfois pas de différence clinique avec Myasthenie sans anti-MusK

Cell-Based Versus Enzyme-Linked Immunosorbent Assay for the Detection of Acetylcholine Receptor Antibodies in Chinese Juvenile Myasthenia Gravis

C. Yan et al. / Pediatric Neurology 98 (2019) 74–79



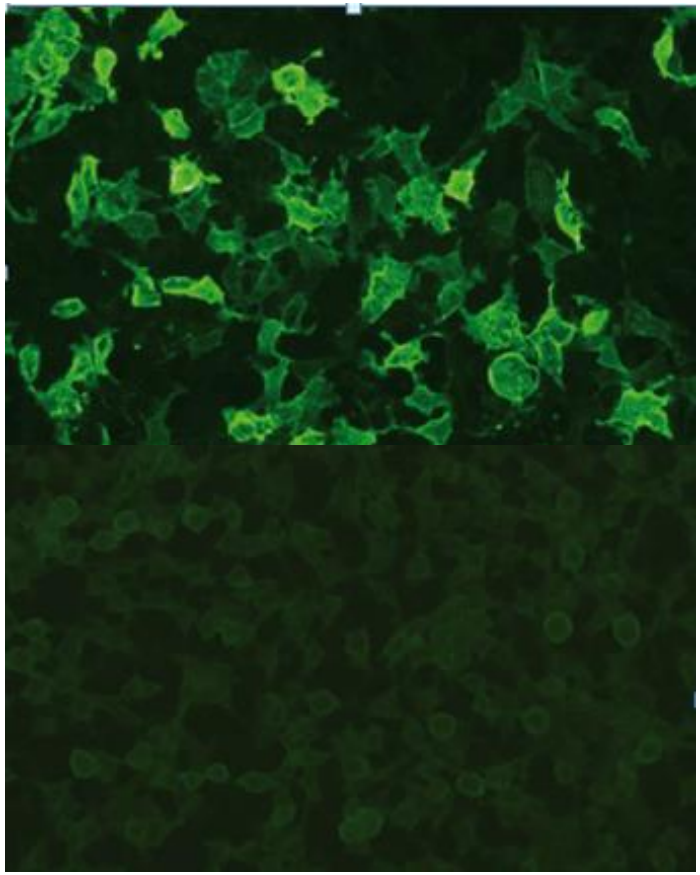
Comparison Among ELISA-Positive, Low-Affinity, and Seronegative Groups

Clinical Information	ELISA and CBA Positive* ($n = 48$)	CBA Positive Only† ($n = 15$)	SNMG‡ ($n = 19$)	P
Gender (F:M)	29: 19	7:8	10:9	0.50§
Age at onset (yr)	4.9 (3.5)	4.5 (2.6)	4.9 (3.7)	0.99‖
Disease duration (mo)	1 (1-72)	3 (1-18)	1 (1-6)	0.09‖
Manifestation				0.50§
OMG	44	15	18	
GMG	4	0	1	

Anti-MuSK en CBA Euroimmun

- IFI avec révélation par anti-**IgG-biotinylée** + avidine-FITC
- 46 patients testés en parallèle avec ELISA anti-MuSK
- Résultats :
  - 100% de concordance
  - Positifs très nets
  - Positifs : clinique pas typique des myasthénies à anti-MuSK : Diplopie binoculaire fluctuante +/- troubles respiratoires

Kit Euroimmun



Bilan

- En 4 années : 4 positifs sur 368 demandes
- Explications :
  - Technique ? RIA (RSR) puis ELISA (IBL)
  - Ethnique ?
  - Sélection des patients ? : étude des dossiers cliniques des demandes d'anti-MuSK et estimation de la probabilité d'une myasthénie
    - Très faible : 47,8%
    - Faible : 26,1%
    - Modérée : 19,6%
    - Prouvée : 6,5%

Conclusions

- Pratiques évoluent
- CBA à évaluer en routine