Cognitive impairment in myasthenia gravis with MuSK antibodies

P.E. Alboini; C. Marra; A. Evoli

Istituto di Neurologia, Università Cattolica del Sacro Cuore – Roma

Introduction

Muscle-specific kinase (MuSK) is a transmembrane protein with a crucial role in synapses formation and signaling. MuSK is composed by an extracellular region with three Ig-Like domain and a frizzled-like domain; a single transmembrane helix connects the ectodomain to the cytoplasmic region, which contains the tyrosine kinase domain (Figure 1).

MuSK, a key-organizer of post-synaptic membrane, was found to be expressed not only in neuromuscular junction, but also in sperm, where it promotes motility, in liver, with an oncogenic role, and in central nervous system (CNS), particularly in the hippocampus and in the cortex (Figure 2) where it is thought to be involved in cholinergic response, synaptic plasticity and memory formation.

Figure 1

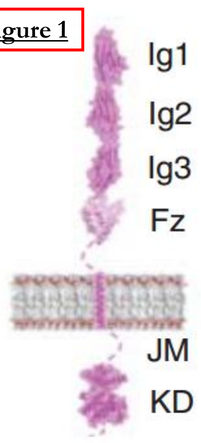
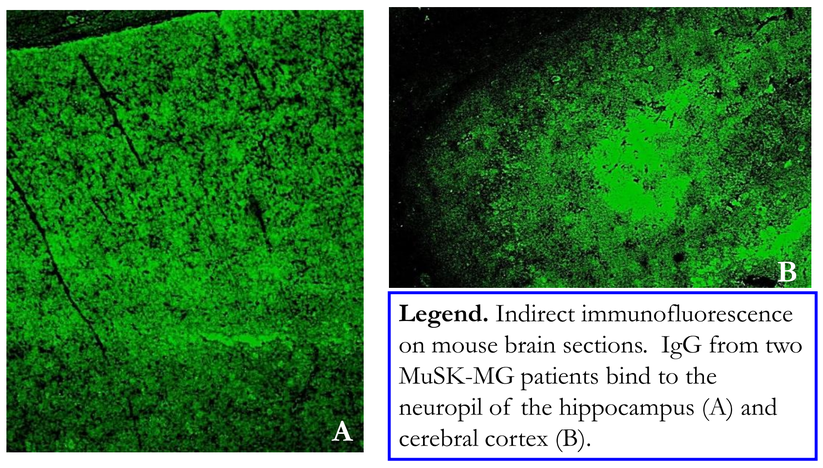


Figure 2



Legend. Indirect immunofluorescence on mouse brain sections. IgG from two MuSK-MG patients bind to the neuropil of the hippocampus (A) and cerebral cortex (B).

Objective

The aim of this study was to evaluate cognitive performances in myasthenia gravis (MG) patients with MuSK antibodies (Abs) and acetylcholine receptor (AChR) Abs, in comparison with healthy controls (HC).

Materials and methods

Cognitive performances were evaluated in:

- 26 MuSK-MG patients (4 males/22 females, aged 40-81 years; mean 57,03);
- 21 AChR-MG patients (3 males/18 females, aged 40-81 years; mean 58);
- 21 HC (8 males/13 females, aged 40-84 years; mean 57,42).

Exclusion criteria: psychiatric illnesses; substance-related disorders; internal diseases that may affect neuropsychological performances (e.g. resistant hypertension, uncontrolled diabetes, liver or kidney failure).

At the time of the study, all MG patients were in good control of their disease, three MuSK-MG patients and a single AChR-MG patient were not taking immunosuppressive treatment, five MuSK-MG and nine AChR-MG patients were under cholinesterase-inhibitor treatment.

Statistical analysis was performed by "One-Way MANOVA".

Neuropsychological evaluation

Subjects enrolled in the study underwent a neuropsychological test battery including the Mini Mental State Examination (MMSE) and an extended version of the Mental Deterioration Battery (MDB), comprehensive of Rey's Auditory Verbal Learning Test (RAVLT), visual and digit span backward-forward, Multiple Features Targets Cancellation (MFTC), Copying Drawings free and joining landmarks, Phonological and Semantic Word Fluency, naming nouns and verbs, Raven's Colored Matrices, Stroop test, trail making test and Free and Cued Selective Remanding Test (FCSRT).

Demographic characteristics

	Age	Education	MMSE
MuSK	57.03 (13.22)	10.53 (3.72)	28.7 (1.86)
AChR	58.00 (10.95)	10.76 (3.75)	29.0 (1.50)
HC	57.42 (14.53)	12.76 (2,94)	29.6 (0.50)
p	0.96	0.21	0.17

No differences in: age, education, gender (p: 0.41), MMSE, MG severity (p: 0.37) and associated diseases

	MuSK	AChR	Tot.
Moderate (MGFA III)	12	7	19
Mild (MGFA I/II)	14	14	28
Tot.	26	21	47

Neuropsychological evaluation cannot be performed in patients with severe disease (classes IV/V MGFA)

References

Garcia-Osta A et al. J Neurosci. 2006 Jul 26;26:7919-7932
Mao Z et al. Ann Indian Acad Neurol. 2015 Apr-Jun;18:131-137
Marra C et al. Muscle Nerve. 2009 Dec;40:952-959
Burden SJ et al. Cold Spring Harb Perspect Biol. 2013;5:a009167

Cognitive tests analysis

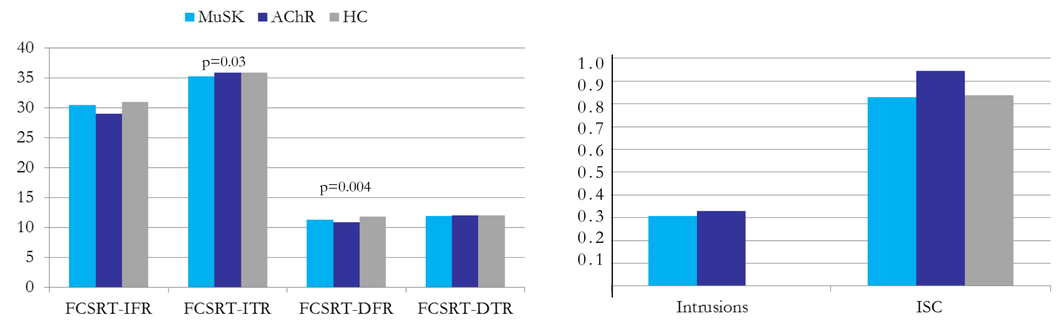
MuSK scored worse in linguisitc tasks

	MuSK		AChR		NC		p
	Media	DS	Media	DS	Media	DS	
RAVLT-IR	43.88	10.57	45.62	9.15	46.86	7.40	0.544532
RAVLT-DR	8.85	3.32	9.10	3.05	10.00	2.26	0.391288
RAVLT-FDR	0.960	0.03	0.958	0.05	0.981	0.02	0.084605
CDS	9.54	2.27	10.33	1.83	10.86	0.85	**0.046155**
CDE	68.35	3.15	69.19	1.81	69.86	0.36	0.069862
Raven	26.69	7.41	27.95	6.22	30.14	3.48	0.157954
Digit span F	6.308	1.64	6.238	1.55	6.857	0.65	0.280125
Digit span B	4.808	1.17	4.381	1.56	5.286	0.72	0.056805
Visual span F	4.423	1.55	4.476	1.17	5.000	0.55	0.219166
Visual span B	4.27	1.31	4.67	1.11	4.57	0.75	0.432770
Stroop-Time	26.92	19.6	19.24	9.2	19.50	7.6	0.099786
Stroop-Error	1.231	2.90	0.452	0.80	0.929	2.33	0.503938
MFTC-Time	60.31	31.00	53.01	23.9	62.29	15.3	0.444001
MFTC-False	0.846	1.93	0.952	4.36	0.286	0.72	0.693204
MFTC-Acc	0.929	0.07	0.949	0.04	0.948	0.08	0.451835
PW Fluency	35.88	12.8	37.10	14.3	40.57	9.1	0.417865
SW Fluency	18.54	6.57	20.43	5.95	25.00	6.10	**0.002874**
Nouns Nam.	28.58	1.79	29.43	0.81	30.00	0.00	**0.000563**
Verbs Nam.	25.50	3.47	27.05	1.63	27.57	0.51	**0.009335**

Free and Cued Selective Reminding Test

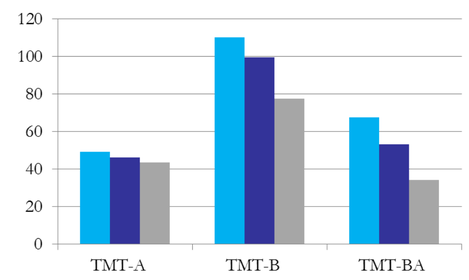
It explores memory recall after semantic cueing

MuSK scored worse in immediate total recall (ITR)



Trail making test

No differences between MuSK, AChR patients and HC

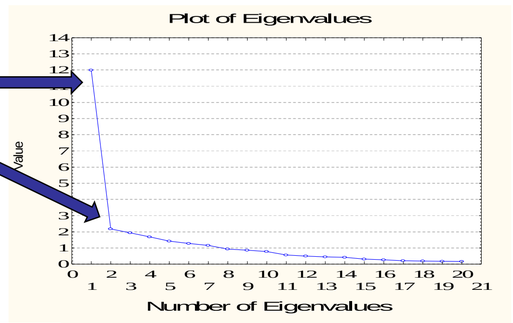


Factor analysis

Two factors :

Factor 1: 43% of generalized variance

Factor 2: 7.8% of generalized variance



Factor 1
RAVLT-IR
Raven
Visual span F
TMT-A
TMT-B
TMT-BA

Factor 2
Nouns naming
Verbs naming
ITR

	AChR	MuSK	p
	Mean	Mean	
Factor 1	0.009602	1.022009	0.923212
Factor 2	2.851737	0.958850	0.091470

→ **MuSK Factor?**

Discussion and conclusion

Cognitive assessment in MG patients did non show real features of dementia, but it allowed to the identify the cognitive tasks, worse than those of normal subjects.

MuSK MG patients showed a specific cognitive impairment in naming nouns and verbs and in recall after semantic cue. These tasks are mediated by hippocampus where MuSK was found to be expressed.

Moreover, it has been demonstrated that agrin, a co-receptor for MuSK, was found to be expressed in blood brain barrier and low density lipopreotein receptor-related 4 (Lrp4) was found to be expressed in hippocampus, where it promotes synaptic plasticity and memory formation. It is acknowledged that MuSK Abs prevent binding between MuSK and Lrp4.

However the exact mechanisms of MuSK activation in the CNS remain still unclear and the occurrence of cognitive impairment in MuSK-MG patients warrants confirmation in further studies.

Sin

XLVII CONGRESSO NAZIONALE
22-25 OTTOBRE 2016 – VENEZIA

WebPoster