Myasthenia Gravis and the COVID-19 pandemics

Marion Boldingh, MD, PhD

Sars-CoV-2 vaccination response in Myasthenia Gravis patients

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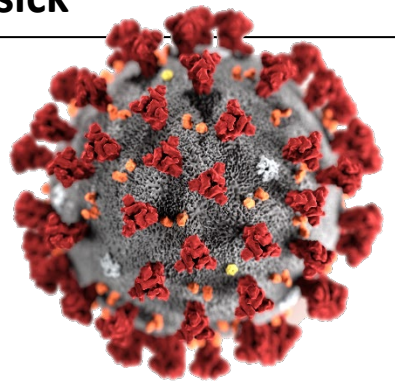
MG and COVID-19

Januar-Februar 2020
COVID-19 was a highly infectious disase

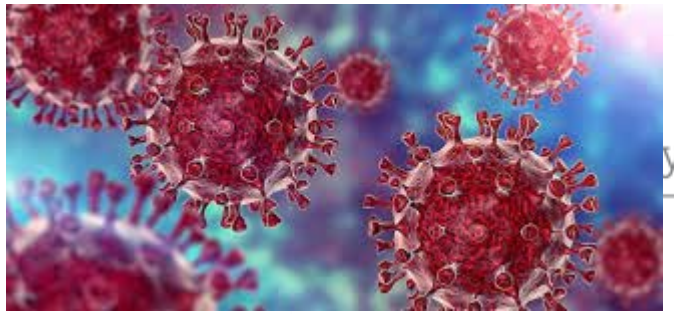
March 2020
Most people don't get severe sick, some get severe sick



MG patients

- Infections can trigger exacerbations
- Often treated by immune therapy that make MG patients vulnerable for infections

With permission from the patient



BRIEF RESEARCH REPORT
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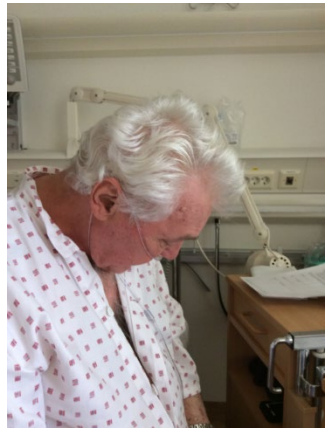
Myasthenia Gravis and COVID-19: Clinical Characteristics and Outcomes

Antonio E. Camelo-Filho[1†], André M. S. Silva[1†], Eduardo P. Estephan[1,2], Antônio A. Zambon[1], Rodrigo H. Mendonça[1], Paulo V. S. Souza[3], Wladimir B. V. R. Pinto[3], Acary S. B. Oliveira[3], Iron Dangoni-Filho[1], Ana F. P. Pouza[1,4], Berenice C. O. Valerio[5] and Edmar Zanoteli[1]*

With permission from the patient



Most MG patient had a serious disease course.
87% intensive care treatment
73% mechanical ventilation
30% mors
Treatment with IVIG and plasmapheresis safe.

Interim analysis oct 2020, n=91

COVID-19-associated risks and effects in myasthenia gravis (CARE-MG)

- MG worsening or crisis requiring resque therapy 40%
- Complete recovery, discharged to home 43%
- Mortality 24%

Impact of COVID and lock down in a cohort of MG patients in India

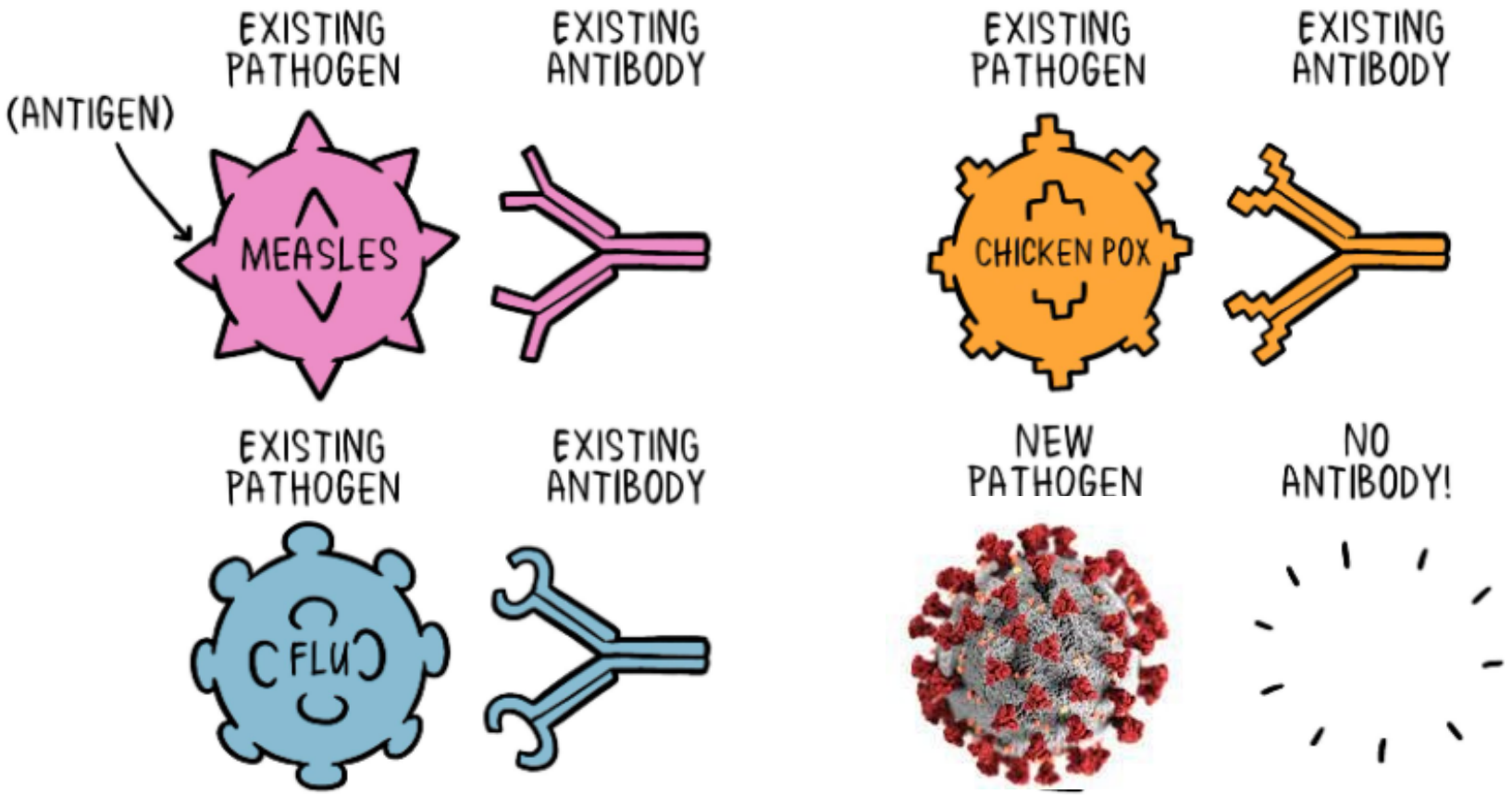
Table 2
Change in Severity of myasthenia gravis, quality of life, activity of daily living, anxiety, depression and quality of sleep a cohort of myasthenia gravis before and after COVID 19 and lockdown.

	Before COVID 19	After COVID 19	P value
HADS score in median and IQR	6 (5,7)	7 (5,8)	0.001
HADS –A in median and IQR	4 (3,5)	2 (1,3.2)	<0.001
HADS –D in median and IQR	2 (1,3)	3 (2,4)	< 0.001
PSQI score in median and IQR	3 (2,4)	4 (3,5)	< 0.001
MGADL score in median and IQR	0.50 (0, 2)	1 (0,3)	<0.001
MGQOL 15 score in median and IQR	6.5 (6,8)	7.5 (610)	0.036
MGFA stage			
IIA	11(28.9 %)	11(28.9 %)	0.71
IIB	10(26.3 %)	10(26.3 %)	
IIIA	17(44.7 %)	15(39.5 %)	
IIIB	0 (0%)	1(2.653 %)	
V	0 (0%)	1(2.65 %)	

A = anxiety, **D**= depression; **HADS** = Hospital Anxiety and Depression Scale; IQR = Inter quartile range; **MGFA** = Myasthenia Gravis Foundation of America; **MG ADL** = Myasthenia Gravis Activity of Daily Living; **MGQOL**= Myasthenia Gravis Quality of Life; **PSQI** = Pittsburgh Sleep Quality Index.

It affected everything
Anxiety
Depression
Sleep qualities
Quality of life

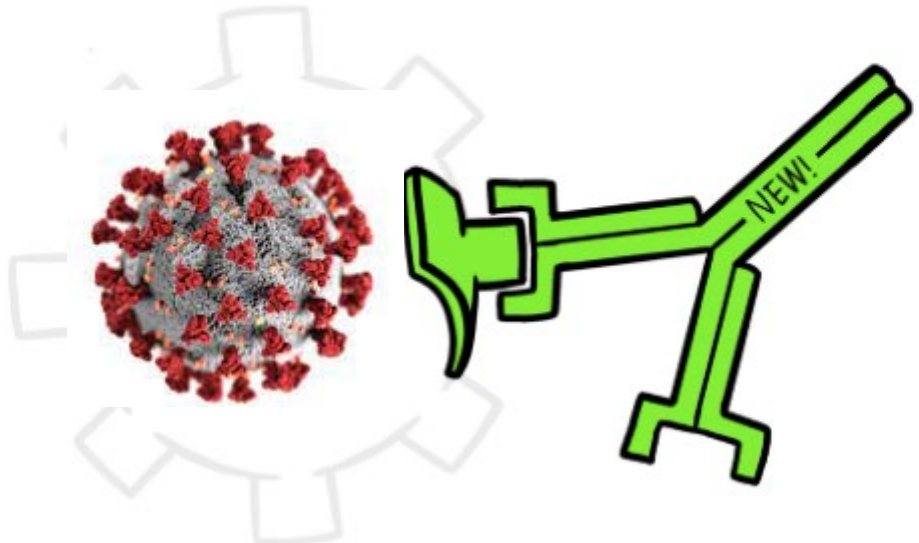
Kalita et al, 2021



When a new pathogen or disease enters our body, it introduces a new antigen. For every new antigen, our body needs to build a specific antibody that can grab onto the antigen and defeat the pathogen.

VACCINE

NEW ANTIBODY



NevroVAX

To Be or Not To Be Vaccinated: That Is a Question in Myasthenia Gravis

*Qian Zhou, Ran Zhou, Haojun Yang and Huan Yang**

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- Lack knowledge among MG patients with and without immune treatment
- Safety and efficacy of vaccination are evaluated among healthy people

Vaccine 35 (2017) 6290–6296

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

A prospective, placebo controlled study on the humoral immune response to and safety of tetanus revaccination in myasthenia gravis

Ellen Strijbos [a,*], Maartje G. Huijbers [a,b], Inge E. van Es [b], Iris Alleman [c], Monique M. van Ostaijen-ten Dam [d], Jaap Bakker [e], Erik W. van Zwet [f], Cornelia M. Jol-van der Zijde [d], Maarten D. van Tol [d], Jan J. Verschuuren [a]

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Response of antibodies after tetanus-revaccination

Effective vaccination response 92% (95% CI 81–98%) of the AChR MG patients.

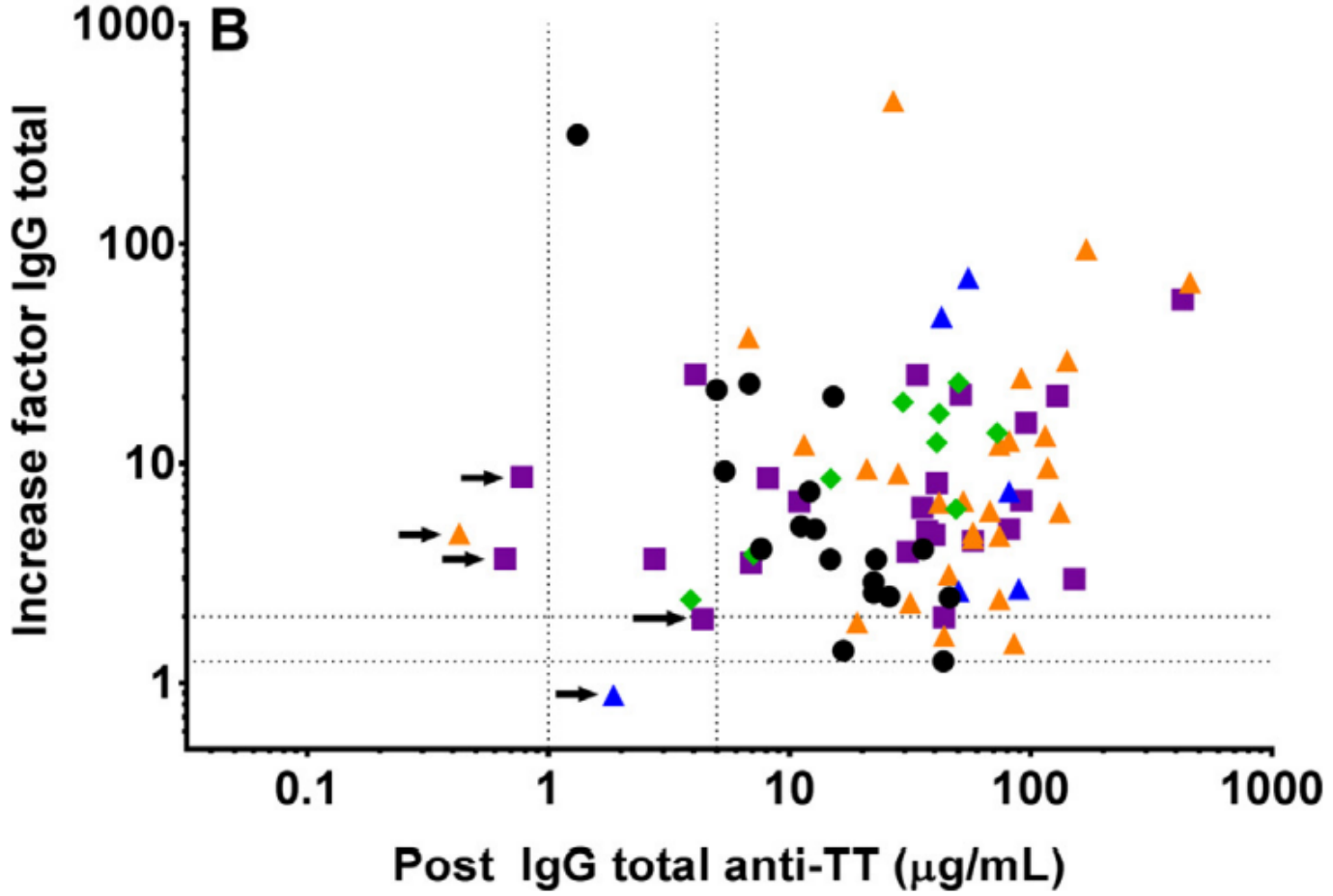
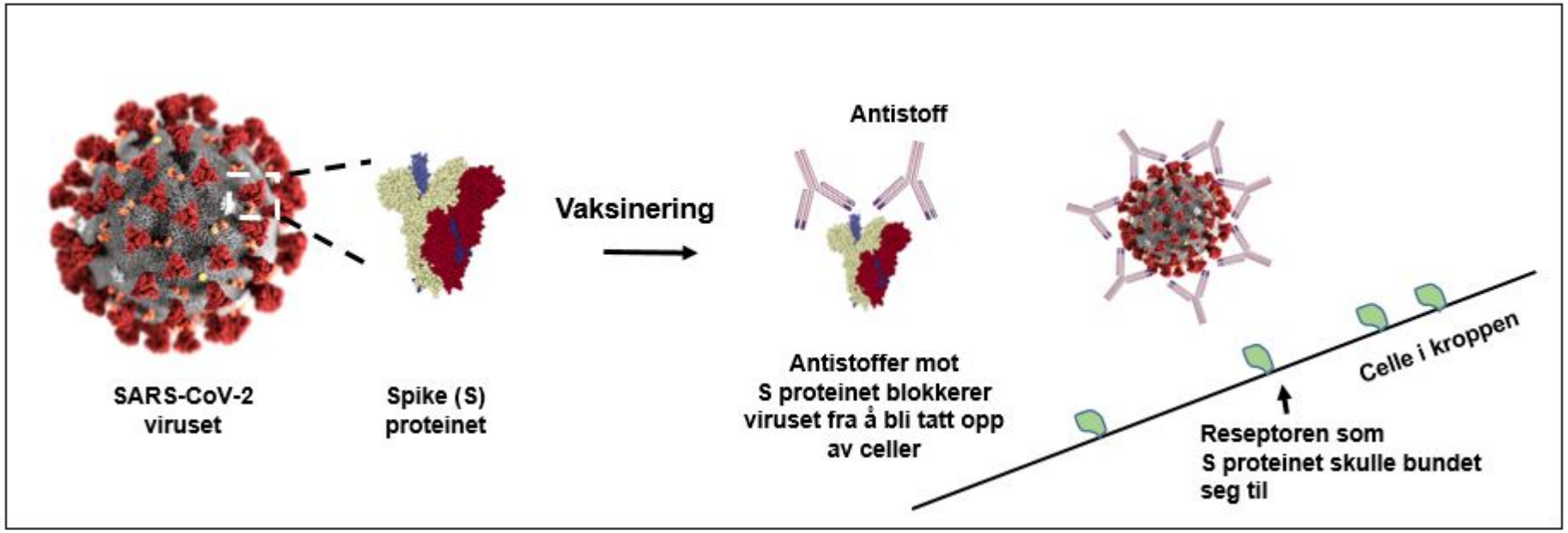


Fig. 2. (**A**) The factor increase of the IgG total anti-tetanus toxoid (TT) titre in the healthy controls (●), in patients with AChR MG with (■) and without immuno-suppressive medication IM (▲) and in the patients with MuSK MG (▲) and LEMS (◆) is dependent on the pre revaccination IgG total anti-TT titre. (**B**) To fulfil the criteria of a significant response, a factor increase of 1.25 or 2 times the pre revaccination IgG total anti-TT titre (horizontal dotted lines) and a post IgG total anti-TT titre > 1 µg/mL or 5 µg/mL (vertical dotted lines), respectively. The arrows indicate patients who don't meet one of these criteria.

Non-responders were 8% (5 / 60 patients)

- AChR MG
  - Prednisolone hhv 15 and 10 mg
- AChR MG
  - Combination of mycophenolate mofetile and sandimmun
  - Musk pas with RTX



Goal: to study vaccination response and safety of COVID-19 vaccines in MG patients

Inclusion criteria: All MG pasienter >18 years at Oslo university hospital

Metods: testing of humoral immune response after 3-12 weeks after fully vaccinated and 3-5 weeks after third vaccination.

Endpoint: IgG levels under 70 BAU/ml= low og IgG levels under 5= no response.

Secondary endpoints: adverse events, change in clinical status and change in medication for MG.

26% none or weak antibody response

- 79 patients checked their anti-RBD IgG - levels after 2. vaccine dose
  - 87% had the Pfizer-vaccine
  - 21/79 (26%) hadde none or weak antibody response
  - Lowest response observed among those who used rituximab, mycophenolate mofetile or high doses of prednisolone.

47.3% had mild-moderate side effects after 2nd vaccine dose.

- **Same as in general population**
- **One with MG crisis and intubation**

	MG pasienter (%)	Pfizer studien(%) (NEJM)	MS (%)
Local reaction	46,4	73.4	47
Fever	16	11	21
Airway symptoms	9		8
Fatigue	29,4	51	40
Headache	25	39	32
Myalgia	27	29	36
vomiting	6	1	9
Lymphoedma	6		4
Home from work	8%		
Anosmia N=1			

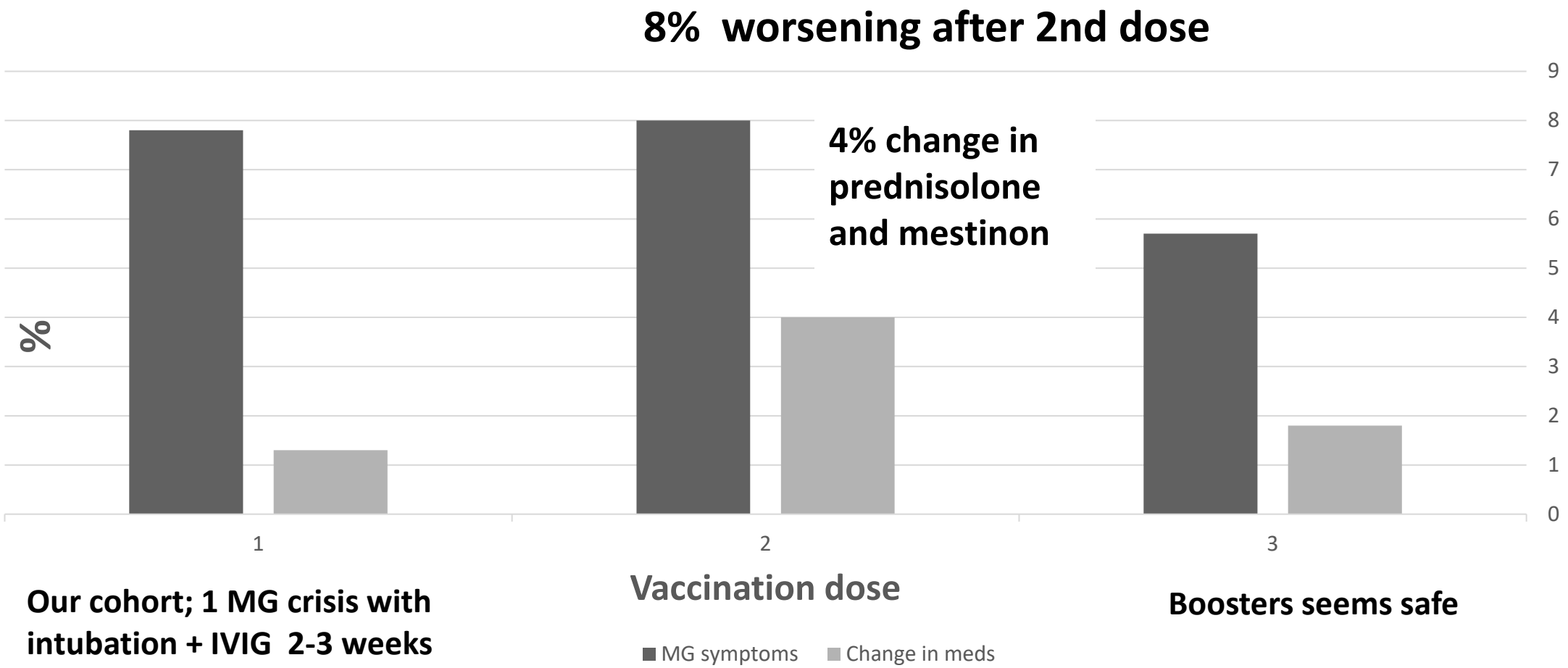
Increased response after third dose

- Pre-vaccination sampling showed that SPIKE-RBD levels had fallen before 3rd dose.

- 58 patients measured their IgG SPIKE levels ca 23 days after 3rd vaccine dose.
- 16% had none or weak immune response (IgG levels under 70 BAU/ml)
- Very bad response: RTX=6, mycophenolate mofetile =3 eller prednisolon>10 mg/d=3.

- Tendency that the IgG levels increased in previously non-RTX non responders.

Change in MG symptoms and medicines



Our cohort; 1 MG crisis with intubation + IVIG 2-3 weeks after vaccination

Boosters seems safe

The literature so far suggests…..

- There may be a 1–15% risk of exacerbation of pre-existing MG following SARS-CoV-2 vaccination, mostly mild and responding well to standard treatment, with the exception of one published case of a patient who suffered a myasthenic crisis one week after the second dose of the Moderna vaccine
- This can be well treated with IVIG, prednisolone or plasmapheresis.
- Our results are in line with these results.

Sansone G, Bonifati DM. Vaccines and myasthenia gravis: a comprehensive review and retrospective study of SARS-CoV-2 vaccination in a large cohort of myasthenic patients. J Neurol 2022;269(8):3965–81. doi:10.1007/ s00415-022-11140-9.

Covid-infection and MG

- The effect size in the vaccine studies **was severe COVID disease or mortality**
  - **No severe COVID 19 disease or mortality among in the cohort.**

- April 2021: Only four patients had had COVID 19 infection before vaccination.
- March 2022: 11% of 84 patients had a breakthrough infection; that means when people get sick even after fully vaccination.
- In this case most likely the omicron VOC, PCR testing was not recommended anymore.

  - Most patient reported worsening of their symptoms.
  - No need for hospitalization.
  - 2/3 reported need for change of MG medication.
  - No information about long COVID in this group.

NevroVAX

MG onset after vaccination

- 42 year old women, no significant medical history, presented with vertical binocular diplopia 3 days after receiving her 2nd dose of moderna vaccine. ACHR abs 1,5 nmol/L and SF-EMG pos. Spontanous recovery 6 months later. No symptoms today.

- 33 year old women, previously Thyroid disease and DM 1, ocular symptoms 3 days after first dose of Pfizer. AChR pos and EMG pos. Generalized symptoms and thymectomized with normal findings.

Research paper

SARS-CoV-2 vaccination and new-onset myasthenia gravis: A report of 7 cases and review of the literature

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Table 1
Characteristics of the 7 new-onset cases with myasthenia gravis (MG) cases in timely association with SARS-CoV-2 vaccination reported in this study. AChR = Acetylcholine receptor antibody; RNS = Repetitive nerve stimulation; SfEMG = Single fibre EMG; PLEX = plasma exchange.

Patient #	Age at onset (years)	Sex	Vaccine	Vaccine dose	Time to symptom onset (days)	Seropostivity	Neurophysiology	MG subtype	Treatment
Patient 1	13	F	Pfizer-BioNTech®	1st dose	14	Negative	RNS – positive	Generalised	Pyridostigmine Prednisolone
Patient 2	59	M	Oxford-Astra Zeneca®	1st dose	2	AChR positive	No data	Generalised	Pyridostigmine Prednisolone
Patient 3	63	M	Pfizer-BioNTech®	3rd dose	3	AchR positive	No data	Ocular	Pyridostigmine
Patient 4	73	M	Pfizer-BioNTech®	3rd dose	12	AChR positive	SfEMG- increasing jitter	Generalised	Pyridostigmine IVIG Prednisolone
Patient 5	50	M	Pfizer-BioNTech®	1st dose	7	AchR positive	RNS -normal	Ocular	Pyridostigmine
Patient 6	83	F	Pfizer-BioNTech®	1st dose	6	AchR positive	RNS -normal SfEMG- not available	Generalised	Pyridostigmine IVIG Prednisolone
Patient 7	77	M	Oxford-Astra Zeneca®	1st dose	3	AchR positive	RNS and SfEMG – Positive	Generalised	Pyridostigmine PLEX Prednisolone

Median time from SARS-CoV-2 vaccination to MG symptom onset was 6 days (IQR 3 to 9.5, range 2–14 days).

Table 2
Characteristics of the 7 previously reported new-onset cases with myasthenia gravis (MG) cases in timely association with SARS-CoV-2 vaccination. AChR = Acetylcholine receptor antibody; RNS = Repetitive nerve stimulation; SfEMG = Single fibre EMG; PLEX = Plasma exchange.

Patient # + Reference	Age at onset	Sex	Vaccine	Vaccine dos	Time to symptom onset (days)	Antibody	Neurophysiology	MG subtype	Treatment
Patient 8 Maher et al	52	M	Oxford-Astra Zeneca®	1st dose	1	Negative	SfEMG positive	Ocular	Pyridostigmine
Patient 9 Galassi et al	73	M	Oxford-Astra Zeneca®	1st dose	8	AChR positive	RNS positive	Ocular	Pyridostigmine
Patient 10 Lee at al	33	F	Pfizer-BioNTech®	2nd dose	1	Negative	RNS positive	Generalised	Pyridostigmine
Patient 11 Chavez et al	82	M	Pfizer-BioNTech®	2nd dose	2	AChR positive	RNS positive	Generalised	Pyridostigmine IVIG Steroids
Patient 12 Watad et al	72	M	Pfizer-BioNTech®	2nd dose	1	No data	RNS positive	Generalised	Prednisolone PLEX
Patient 13 Watad et al	73	M	Pfizer-BioNTech®	2nd dose	7	No data	RNS positive SfEMG- positive	Generalised	Pyridostigmine PLEX Prednisolone
Patient 14 Sansone et al	64	F	Pfizer-BioNTech®	2nd dose	12	No data	No data	No data	No data

Median time from SARS-CoV-2 vaccination to MG symptom onset was 2 days (IQR 1–7.5, range 1–12). Two patients (Patients 9 and 11) required intensive care support due to bulbar and respiratory failure

Serum Acetylcholine Receptor Antibodies Before the Clinical Onset of Myasthenia Gravis

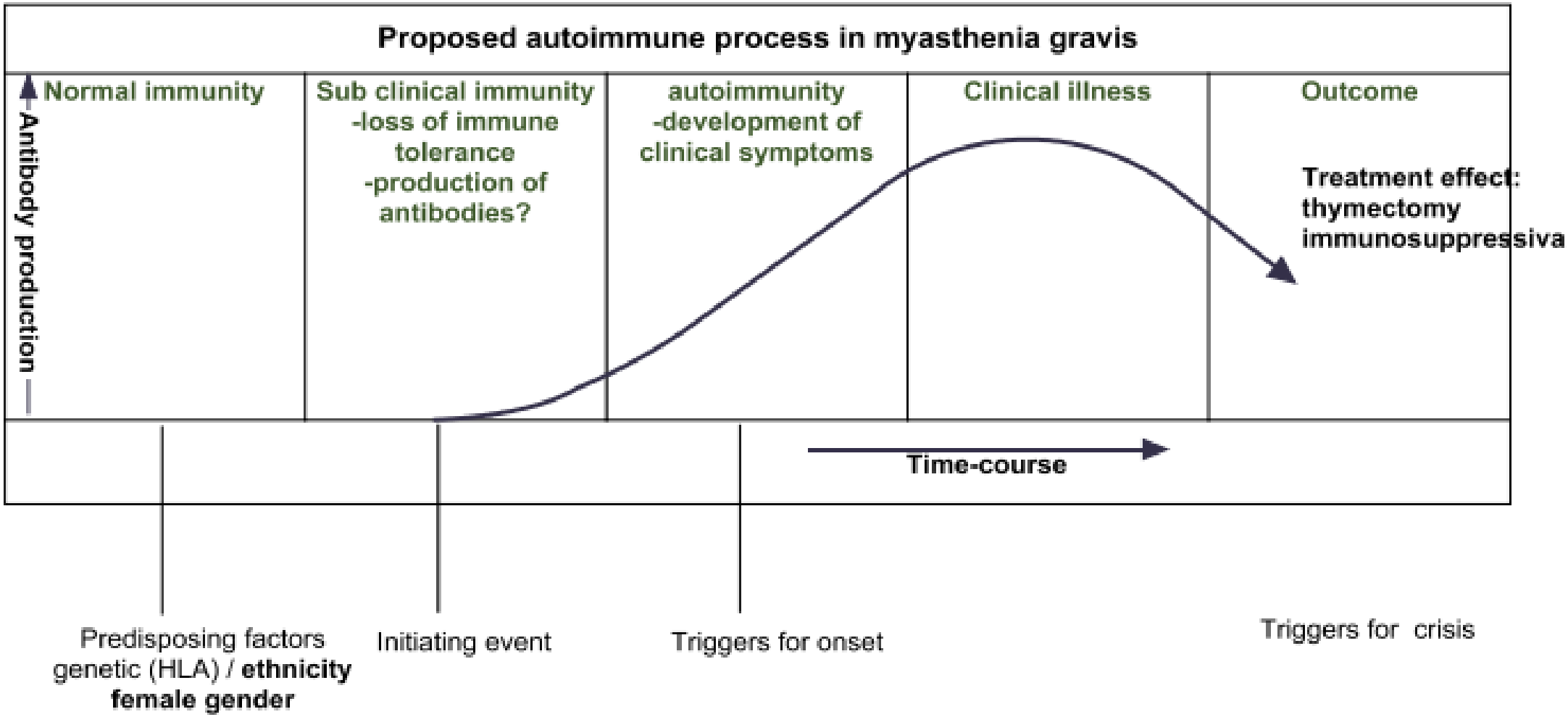
Cite

Article type: Case Report

Authors: Strijbos, Ellen[a;*] | Verschuuren, Jan J.G.M.[a] | Kuks, Jan B.M.[b]

Affiliations: [a] Department of Neurology, Leiden University Medical Centre, The Netherlands | [b] Department of Neurology, University Medical Centre of Groningen, The Netherlands

Authors stated: Developing a disease so fast, leads to the thought that unmasking an subclinical autoimmune response is the most likely explanation



Diabetes and thyroid disease, female gender

Vaccination

Development of manifest disease

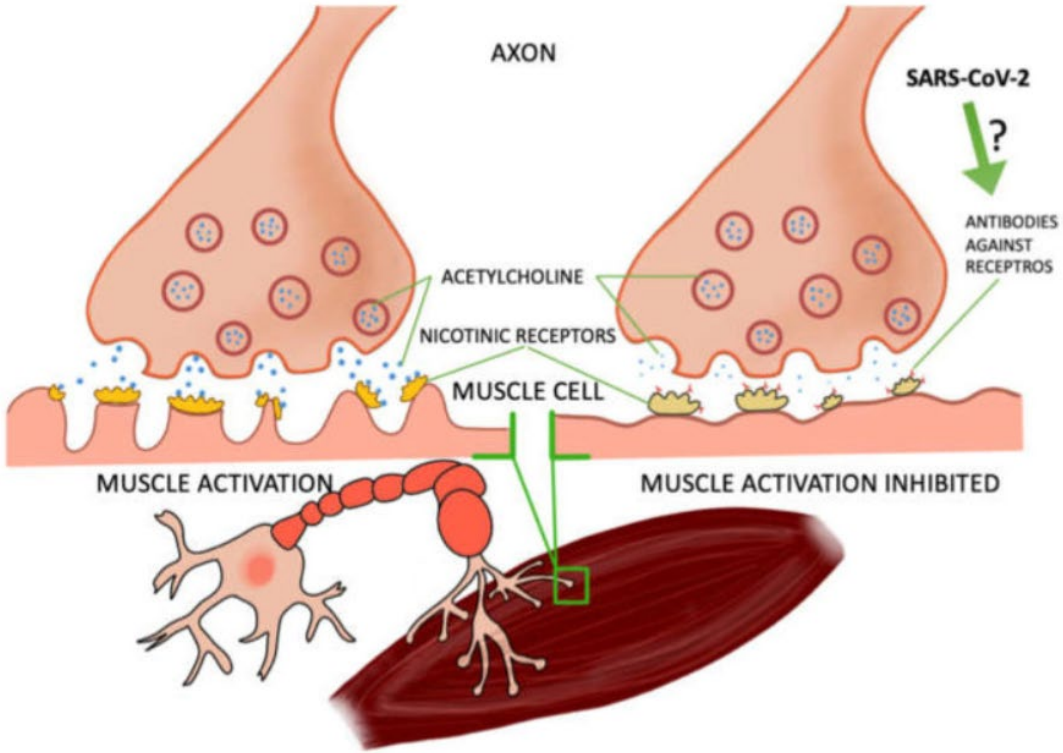
International Journal of
Molecular Sciences

NeuroCOVID

Review

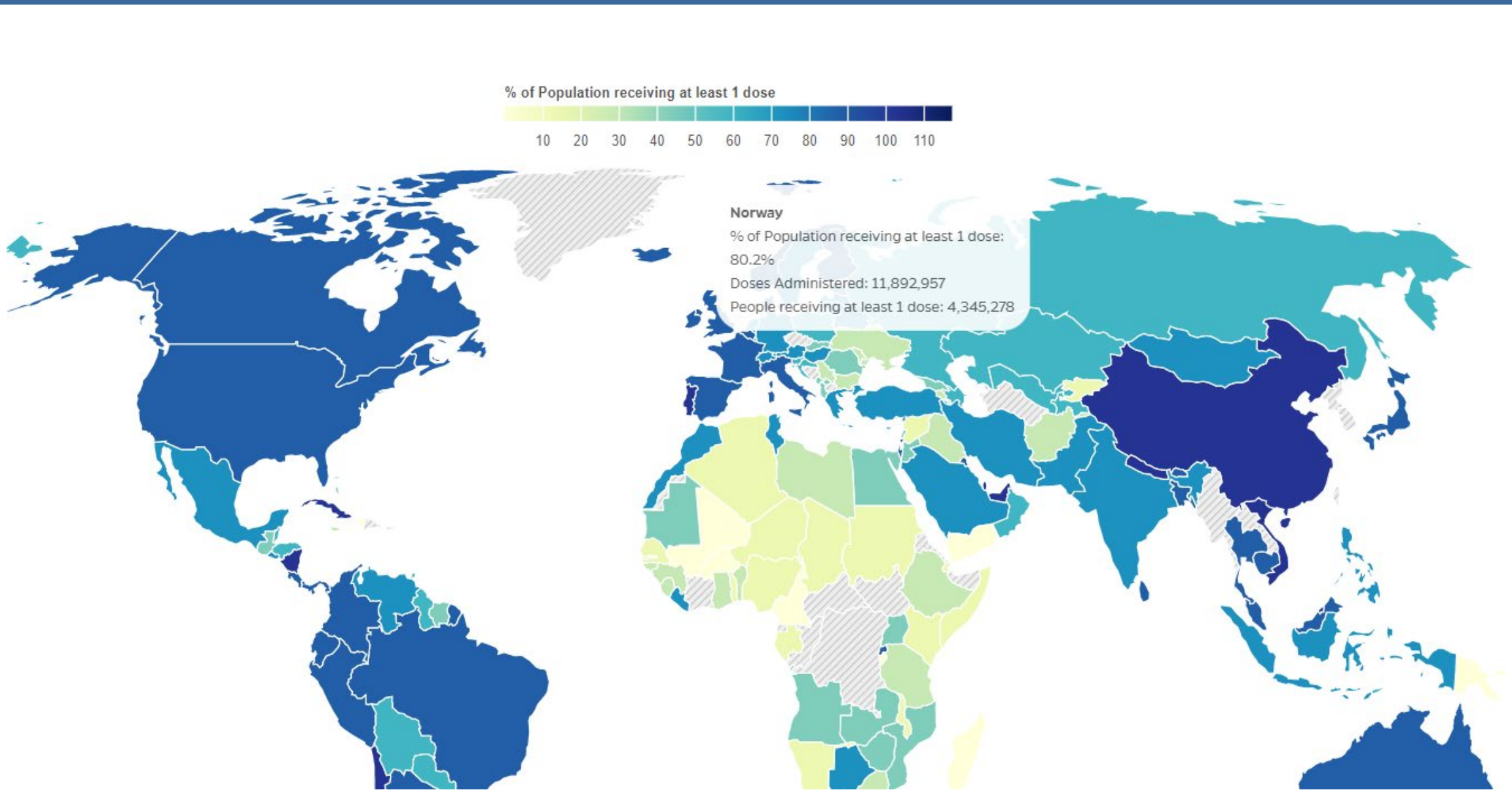
Disorders of the Cholinergic System in COVID-19 Era—A Review of the Latest Research

Marta Kopańska [1,*], Marta Batoryna [2], Paulina Bartman [3], Jacek Szczygielski [4,5] and Agnieszka Banaś-Ząbczyk [6]



Post-Covid diplopia 1-2 weeks
Spontanous recovery,
No MG diagnosis

Discovered that the Sars-CoV-2 SPIKE protein which is build after COVID or vaccination has a sequence which is able to bind on the nicotinic receptor, thus mimicing MG disease.


% of Population receiving at least 1 dose
10 20 30 40 50 60 70 80 90 100 110
Norway
% of Population receiving at least 1 dose:
80.2%
Doses Administered: 11,892,957
People receiving at least 1 dose: 4,345,278

General recommendation when to vaccinate www.fhi.no

- Most important is to vaccinate
- When using azathioprine, prednisolone, mycophenolate mofetile, sandimmun and methotrexate- just take the vaccine
- When using immunoglobulins- wait for 1-2 weeks after infusion
- When using RTX, take the vaccine 2 weeks before or as long as possible after.
- Not combining more vaccines at the same time.

Summary

- Vaccine seems safe in MG patients
- Patients with RTX do not mount an immune responses to COVID-19 vaccines at all→ anti-viral therapy ?
- Patients with high doses prednisolone, combinations therapies and mycophenolate mofetile benefits from booster doses
- Booster needed and recommended in all patients
- Breakthrough infections in vaccinated MG patients have good outcomes (at least with omicron VOC)
- Vaccination can trigger MG disease in susceptible individuals