Neurology Perspectives 5 (2025) 100193

NEUROLOGY PERSPECTIVES

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LETTER TO THE EDITOR

Myasthenic crisis probably triggered by local lidocaine infiltration unveiling generalized myasthenia gravis without extraocular muscle involvement

Crisis miasténica probablemente desencadenada por infiltración local de lidocaína revelando una miastenia gravis generalizada sin afectación de la musculatura extraocular

Dear Editor,

Myasthenia gravis (MG) is an autoimmune disease due to antibodies against the acetylcholine receptor (AChR) (80%), muscle-specific kinase (MuSK), or other AChR-related proteins in the postsynaptic muscle membrane.[1] Fifteen percent of patients have ocular symptoms only, whereas 85% develop more generalized MG (gMG) including non-ocular muscle weakness.[1] Diagnosis is straightforward in patients with typical symptoms and positive antibodies. Detailed clinical and neurophysiological examination is important in antibody-negative patients and to confirm neuromuscular junction dysfunction, without waiting for antibody results.[1]

Other autoimmune conditions like systemic lupus erythematosus (SLE), rheumatoid arthritis, thyroid dysfunction, and diabetes mellitus (DM) are present in up to 10% of patients.[2] Immunosuppressants, thymectomy, and acetylcholinesterase inhibitors constitute therapeutic cornerstones.[1,3] MG prognosis is usually good, although myasthenic crisis (MC) defined by respiratory insufficiency that requires the need for respiratory support represents a life-threatening complication.[3] MC can be due to bulbar weakness with upper airway collapse.[4] MC occurs in 15–20% of MG patients, with a mortality of 4.5%.[4]

We report a novel case of MC probably triggered by local lidocaine infiltration revealing gMG without extraocular muscle involvement.

A 68-year-old woman presented a 6-month history of symmetrical and proximal weakness first in upper limbs and then lower limbs, fatigability, hyperCKemia (229 IU/L), and mixed dysphagia. She had a history of allergy to iodinated contrasts, tobacco abuse, well-controlled arterial hypertension, dyslipidemia, rheumatic mitral stenosis, paroxysmal valvular atrial fibrillation, acute myocardial infarction, and SLE. She was receiving oral atorvastatin 40 mg/24 h, esomeprazole 20 mg/24 h, acenocoumarol (total weekly dose: 7 mg), valsartan/hydrochlorothiazide 80/12.5 mg/24 h, deflazacort 12 mg/24 h, hydroxychloroquine 300 mg/24 h, and subcutaneous belimumab 200 mg/week. Her family medical history was unremarkable. Needle electromyography (EMG) findings from another center were suggestive of myopathy because motor unit action potentials (MUAPs) were short in duration and low in amplitude, but without polyphasia, with normal recruitment, without spontaneous activity (we only had the conclusion of the EMG report, but not the complete description neither the tables or images of the results).

She was admitted to our hospital for a muscle biopsy of the left deltoid muscle. Just following subcutaneous lidocaine infiltration (8 mL [10 mg/mL], that is, 80 mg), she suffered acute respiratory failure, with decreased consciousness, tetraplegia (sparing feet), and facial diplegia, requiring orotracheal intubation and admission to the ICU. Urgent EEG, brain CT, and CTA were normal. Neurological evaluation disclosed spared extraocular muscle, pupils, deep tendon reflexes, and sensory function. Given the suspicion of MG, neostigmine test was performed showing slight improvement in facial diplegia. Urgent repetitive nerve stimulation and single-fiber electromyography (SFEMG) were performed. Repetitive stimulation of the right ulnar nerve at 3 Hz demonstrated typical decrement (Fig. 1). SFEMG of the right extensor digitorum and frontalis muscles showed increased mean jitter (Fig. 2). Whole-body CT, sensory-motor conduction studies, and needle electromyography findings were unremarkable. The patient was started on intravenous immunoglobulin (IVIG) (1 g/kg/24 h) for 2 days, with subsequent maintenance with nasogastric pyridostigmine 60 mg/6 h, obtaining progressive weakness improvement, persisting mixed dysphagia. Four days later, after clinical and hemodynamic stabilization, she was

https://doi.org/10.1016/j.neurop.2025.100193

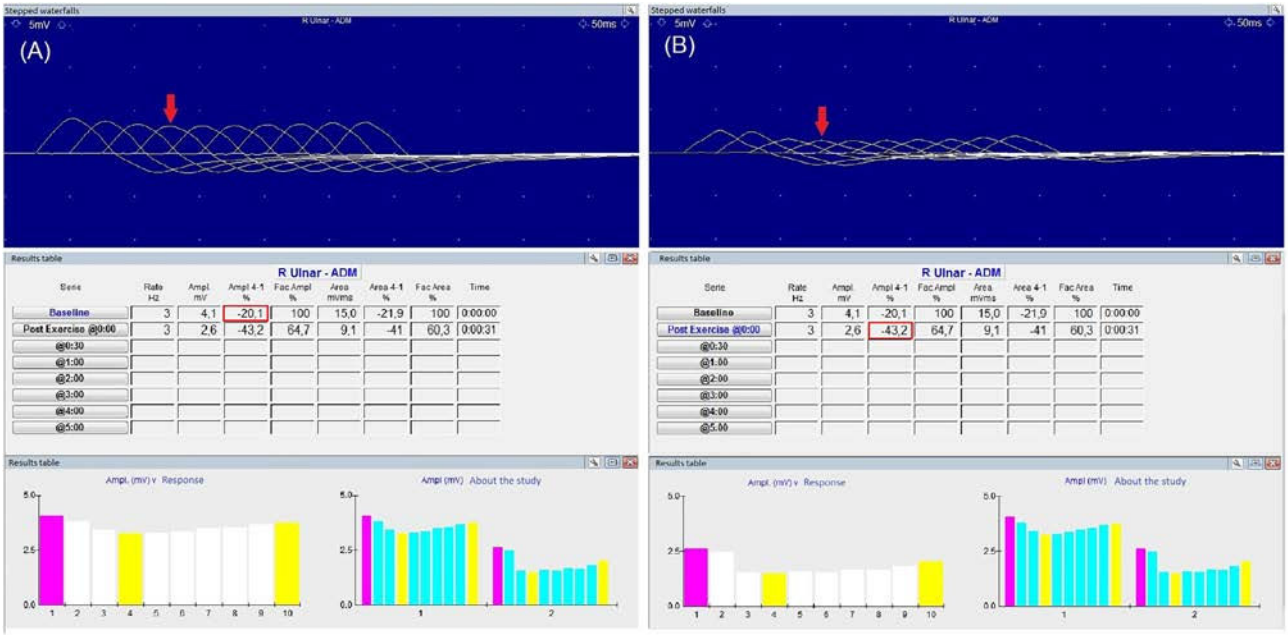


Figure 1 Repetitive nerve stimulation. Low-frequency repetitive nerve stimulation (RNS) at 3 Hz of the right (R) ulnar nerve recording from abductor digiti minimi revealed 20.1% (red box) decrement in amplitude from the first to the fourth compound muscle action potential (CMAP) (red arrow), corresponding to clinical muscle fatigability (A). And a maximal 43.2% (red box) decrement 2 min after exercise lasting 1 min (red arrow) (B). These results are suggestive of postsynaptic neuromuscular junction disorder. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

discharged from the ICU to the ward, requiring nasogastric tube feeding. Eight days later, a positive result of anti-AChR antibodies (>20 nmol/L) was received, confirming gMG diagnosis. The rest of the laboratory results were normal (except for steroid-induced DM).

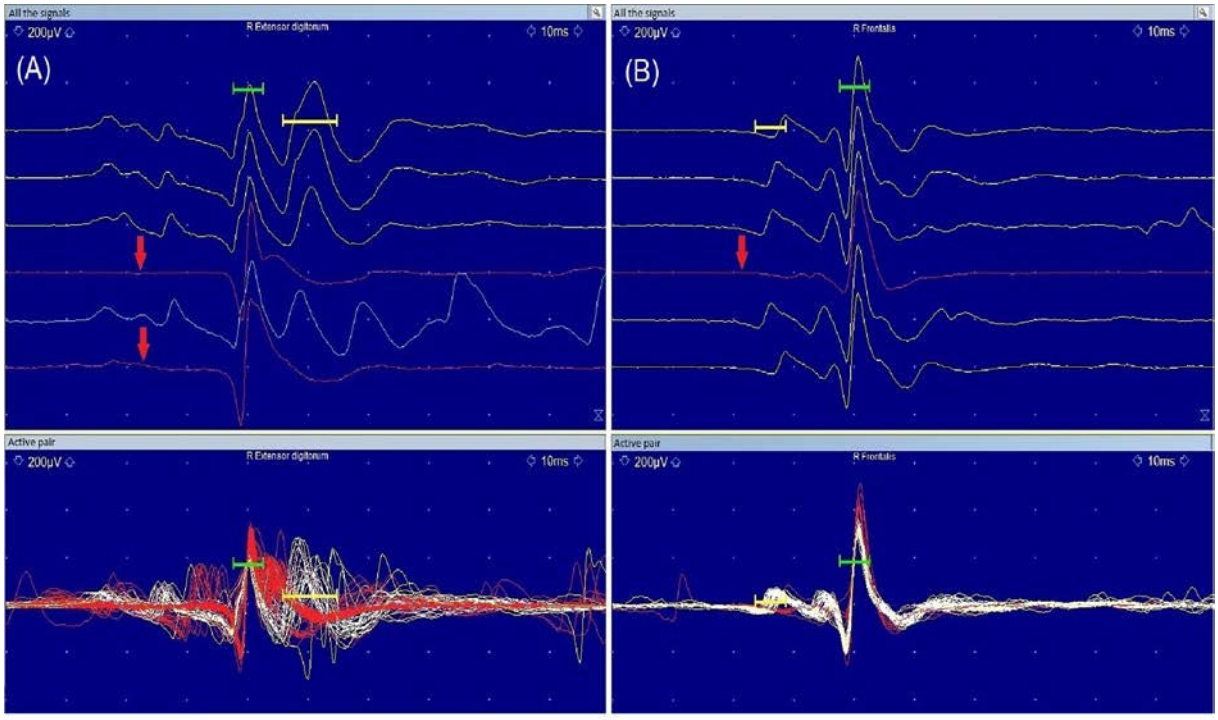
Two weeks later, due to generalized worsening of muscle strength (without respiratory failure) associated with *Citrobacter freundii* urinary tract infection, she received IVIG again (1 g/kg/24 h) for 2 days, with remarkable muscle strength improvement, including dysphagia, tolerating orally. Currently, she continues undergoing physiotherapy daily as an outpatient, without new myasthenic crises since then, remaining clinically and hemodynamically stable, with follow-up in Neurology consultations.

Several triggers for MC have been described: respiratory infections (the most common), stress, treatment discontinuation, surgery, trauma, pregnancy/postpartum, corticosteroids, antibiotics (e.g., aminoglycosides, macrolides, and quinolones), statins, etc.[4,5] When possible, local/regional anesthesia should be used.[6] However, local procaine, lidocaine, and bupivacaine may worsen MG,[6] since transmission of the neural impulse (action potential) to the resting muscle may be blocked and disrupted with local anesthetic drugs, thus worsening existing MG or triggering MC.[7] Indeed, there is experimental evidence that local lidocaine can potentiate the effect of neuromuscular blocking drugs through presynaptic (impairment in the quantal release of acetylcholine with a decrease in the safety margin of the neuromuscular junction) and postsynaptic (significant decrease in the contracting response to acetylcholine and reduced sensitivity of the postjunctional membrane to acetylcholine) effects, evaluated in *chick biventer cervicis* preparations, demonstrated by a significant decrease in the contracting response to acetylcholine. This may suggest a competitive mechanism between the local anesthetic and the neurotransmitter.[8–10]

MG course is marked by exacerbations and remissions.[2] IVIG and plasma exchange (PE) are considered equivalent in MC treatment.[1,3] The decision for IVIG or PE will depend on concomitant diseases and availability (these features favored IVIG in our case).[3] IVIG should be administered at 0.4 g/kg body weight (bw) for five consecutive days, alternatively 1 g/kg bw for 2 days (as in our case).[3]

To our knowledge, this is the first reported case of MC following local lidocaine infiltration unveiling anti-AChR-positive gMG without extraocular muscle involvement. Although other concomitant medications such as atorvastatin, corticosteroids, or hydroxychloroquine (chronically administered) are known to worsen MG, lidocaine systemic diffusion (due to the vasodilator properties of lidocaine which are believed to occur due to the inhibition of action potentials via sodium channel blocking in vasoconstrictor sympathetic nerves)[11] was the most likely cause of MC given its close temporal relationship, with a score of 7/13 in the Naranjo algorithm for adverse drug reactions.[12]

Nevertheless, two major limitations of this study should be taken into account. First, we report a single case. Second, although they were minimal, stress related to surgery (muscle biopsy) and the surgical procedure itself could have contributed to the MC (because of this, we say "probably triggered by local lidocaine infiltration"). Anyway, clinicians should be aware of this exceptional but life-threatening possible adverse event.



SFEMG - Volitional

Muscle		N	Jitter µs	MIPI µs	MCD µs	MSD µs	Block	Firing Rate Hz
(A) R Extensor digitorum	Nº of pairs	5						
	% Blocked						100	
	Mean		228	1363	228	269	-	16
	Median		170	980	170	175	-	16
	1.1 Pair	102	97	1186	97	98	31	16
	2.1 Pair	149	315	941	315	373	81	21
	3.1 Pair	62	490	897	490	621	34	19
	4.1 Pair	103	69	980	69	78	0	13
	5.1 Pair	44	170	2812	170	175	9	13
(B) R Frontalis	Nº of pairs	4						
	% Blocked						100	
	Mean		100	978	108	101	-	13
	Median		96	1007	102	98	-	12
	1.1 Pair	51	86	1373	97	86	8	12
	1.2 Pair	121	107	524	107	111	42	12
	2.1 Pair	84	63	1026	66	63	10	13
	3.1 Pair	65	146	987	160	146	18	15

Figure 2 Single-fiber electromyography (SFEMG). Volitional (voluntary) SFEMG recorded by concentric needle electrodes in the right (R) extensor digitorum (ED) (A) and frontalis (FR) (B) muscles found remarkably increased mean jitter (ED: 228 µs [upper limit 30 µs],[13] FR: 100 µs [upper limit 28 µs],[13] highlighted in yellow) with 100% impulse blocking in both muscles, showing a severe impairment of the postsynaptic neuromuscular junction of generalized distribution, suggestive of generalized myasthenia gravis. The jitter value was calculated by the mean consecutive difference (MCD) for each pair. We were able to study only five pairs in the R ED and four in the R FR due to the patient's clinical and hemodynamic instability. Usually, two subtypes of SFEMG are used to diagnose MG: 1) Voluntary SFEMG measures the variability in activation time (jitter) between muscle fibres that are innervated by the same motor axon when the patient voluntary contracts the muscle, and 2) Stimulation SFEMG measures variability between the time of nerve stimulation and muscle response (jitter).[1] Jitter for each pair of potentials can be expressed as the MCD and as the mean sorted difference (MSD).[13]MIPI: mean interpotential interval; N: total number of observations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

In our case, despite MC occurrence, early identification and prompt ICU management through an interdisciplinary approach involving intensive care and internal medicine doctors, neurologists, and clinical neurophysiologists prevented the development of further complications. Further case series addressing our case limitations are warranted to shed light on the epidemiology, risk factors (e.g., positive anti-AChR antibodies), and dose range associated with MC following local lidocaine infiltration.

Informed consent

Written informed consent was obtained from the patient participating in the study (consent for research).

Ethical considerations

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines

Study funding

Nil.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

J. Benito-León is supported by the National Institutes of Health (NINDS #R01 NS39422 and R01 NS094607) and the Recovery, Transformation, and Resilience Plan of the Spanish Ministry of Science and Innovation (grant TED2021-130174B-C33 and NETremor and grant PID2022-138585OB-C33, Resonate).

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