La Disfagia Neurogena: trattamento con tossina botulinica

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Dysphagia 19:52–57 (2004)
DOI: 10.1007/s00455-003-0029-3

Dysphagia
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Prolonged Effect of Botulinum Toxin Injection in the Treatment of Cricopharyngeal Dysphagia: Case Report and Literature Review

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[1]Department of Neurology, [2]Department of Medical Imaging, [3]Department of Otolaryngology, National Taiwan University Hospital, College of Medicine, National Taiwan University, Taipei, Taiwan

Schenider I, Thumfart WF, Potoschig C, *et al*. Treatment of dysfunction of the cricopharyngeal muscle with botulinum A toxin: introduction of a new, noninvasive method. *Ann Otol Rhinol Laryngol* 1994;**103**:31–5.

Haapaniemi JI, Laurikainen EA, Pulkkinen J, *et al*. Botulinum toxin in the treatment of cricopharyngeal dysphagia. Review of the use of botulinum in treating proximal dysphagia. *Dysphagia* 2001;**16**:171–5.

Ahsan SF, Meleca RJ, Dworkin JP. Botulinum toxin injection of the cricopharyngeus muscle for the treatment of dysphagia. *Otolaryngol Head Neck Surg* 2000;**122**:691–5.

Blitzer A, Sulica L. Botulinum toxin: basic science and clinical uses in otolaryngology. *Laryngoscope* 2001;**111**:218–26.

Restivo DA, Palmeri A, Marchese-Ragona R. Botulinum toxin for cricopharyngeal dysfunction in Parkinson's disease. *N Engl J Med* 2002;**346**:1174–5.

Merlo IM, Occhini A, Pacchetti C, *et al*. Not paralysis, but dystonia causes stridor in multiple system atrophy. *Neurology* 2002;**58**:649–52.

Botulinum Toxin Is Effective in the Management of Neurogenic Dysphagia. Clinical-Electrophysiological Findings and Tips on Safety in Different Neurological Disorders

Enrico Alfonsi[1], Domenico A. Restivo[2], Giuseppe Cosentino[3], Roberto De Icco[1,4], Giulia Bertino[5], Antonio Schindler[6], Massimiliano Todisco[1,4], Mauro Fresia[1], Andrea Cortese[1], Paolo Prunetti[1,4], Matteo C. Ramusino[1,4], Arrigo Moglia[1,4], Giorgio Sandrini[1,4] and Cristina Tassorelli[1,4]*

The Role of Botulinum Toxin Injection and Upper Esophageal Sphincter Myotomy in Treating Oropharyngeal Dysphagia

Giovanni Zaninotto, M.D., F.A.C.S., Rosario Marchese Ragona, M.D., Chiara Briani, M.D., Mario Costantini, M.D., Christian Rizzetto, M.D., Giuseppe Portale, M.D., Lia Zanetti, M.D., Stefano Masiero, M.D., Michela Costantino, Ph.D., Loredana Nicoletti, R.N., Alessandro Polidoro, R.N., GianPiero Feltrin, M.D., Corrado Angelini, M.D., Ermanno Ancona, M.D., Diego Guidolin, Ph.D., Anna R. Parenti, M.D.

ity at VFS and an intact bolus propulsion ability on manometry. (J Gastrointest Surg 2004;8:997–1006) © 2004 The Society for Surgery of the Alimentary Tract

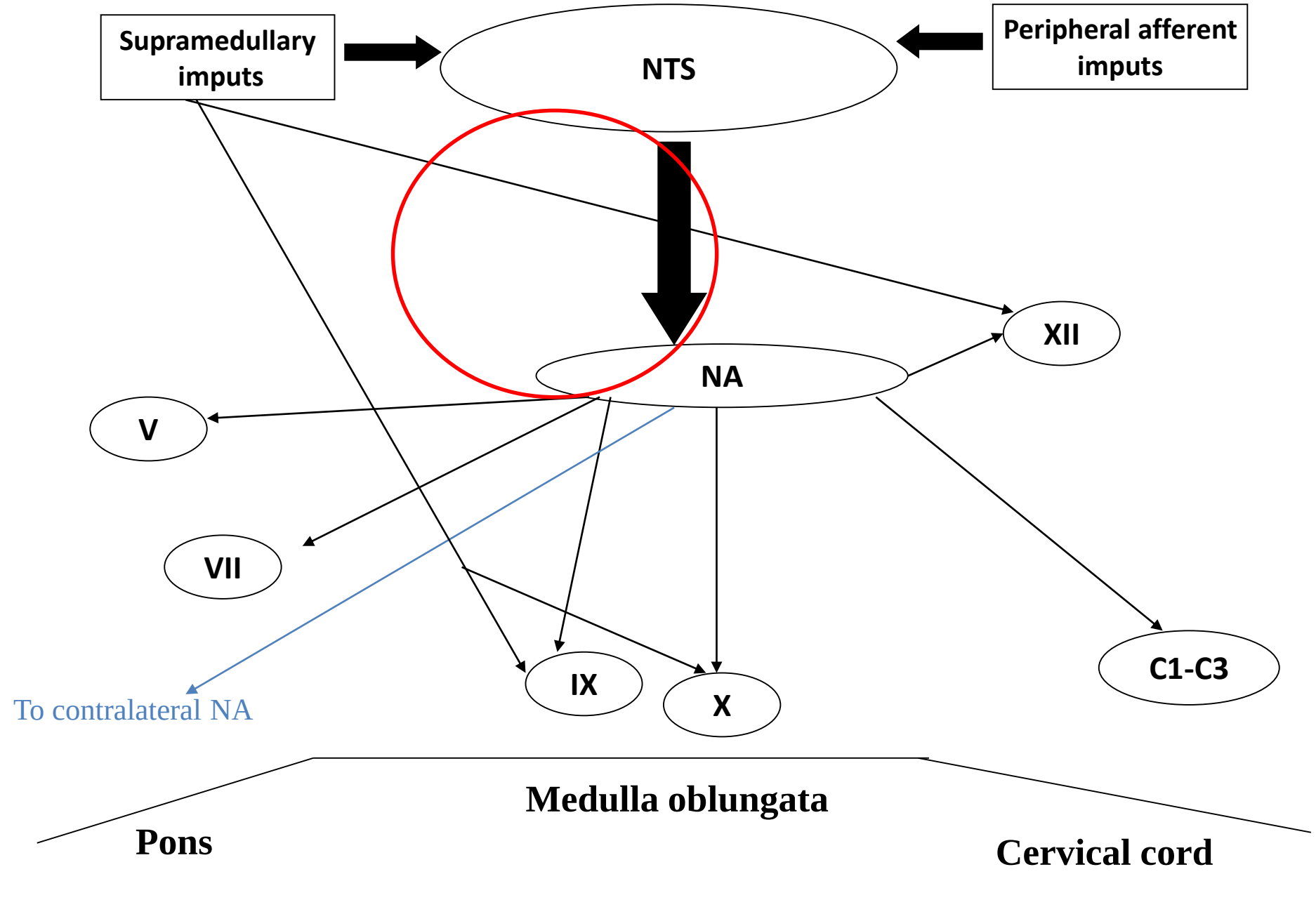
An electrophysiological approach to the diagnosis of neurogenic dysphagia: implications for botulinum toxin treatment

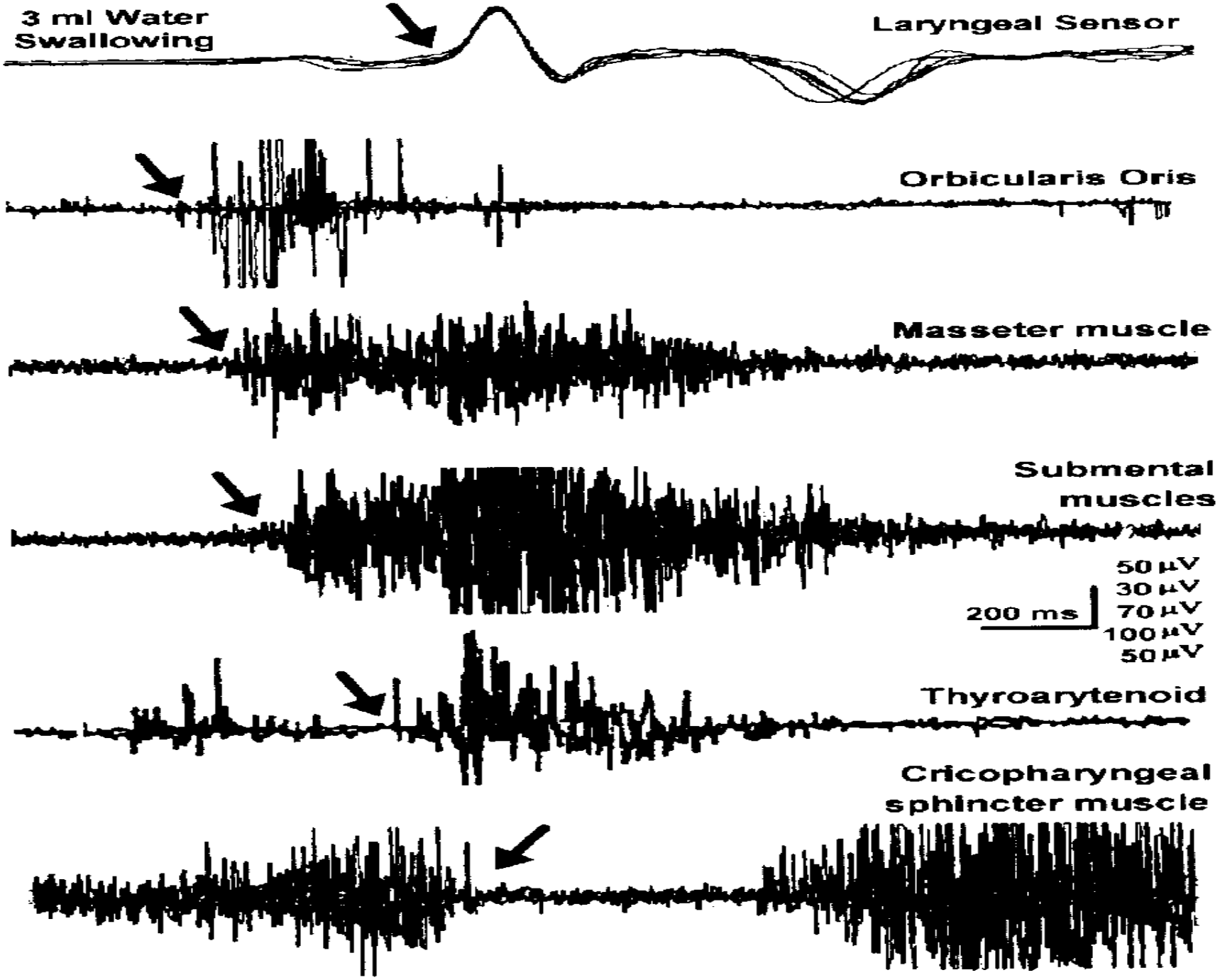
E Alfonsi,[1] I M Merlo,[1] M Ponzio,[2] C Montomoli,[2] C Tassorelli,[3] C Biancardi,[1] A Lozza,[1] E Martignoni[4]

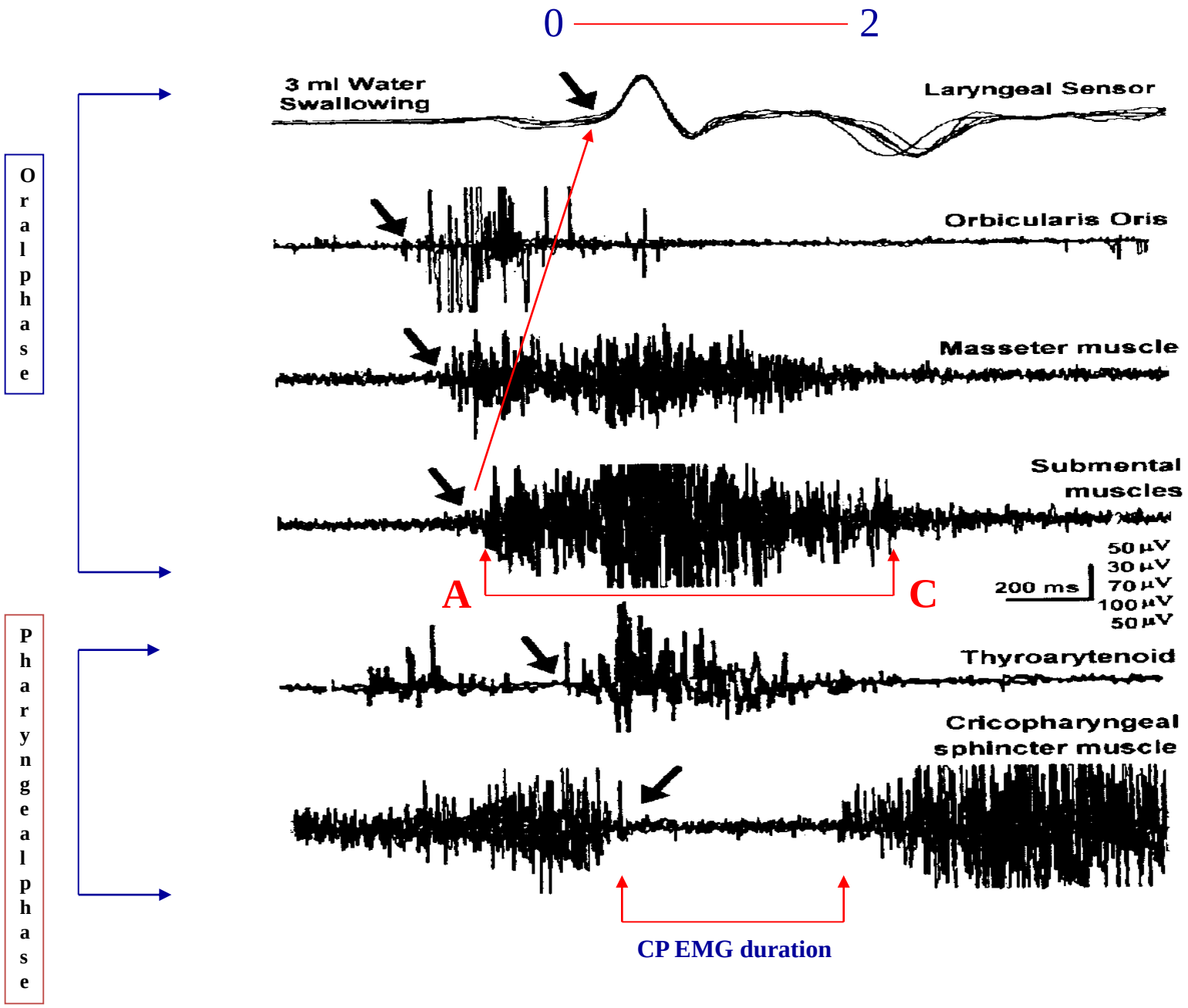
J Neurol Neurosurg Psychiatry 2010;**81**:54–60.

‘Swallowing is a complex process regulated by a trigger center in the brainstem, the central program generator (CPG), which receives imput from the cerebral cortex and peripheral muscles and directs the final sequence of swallowing’

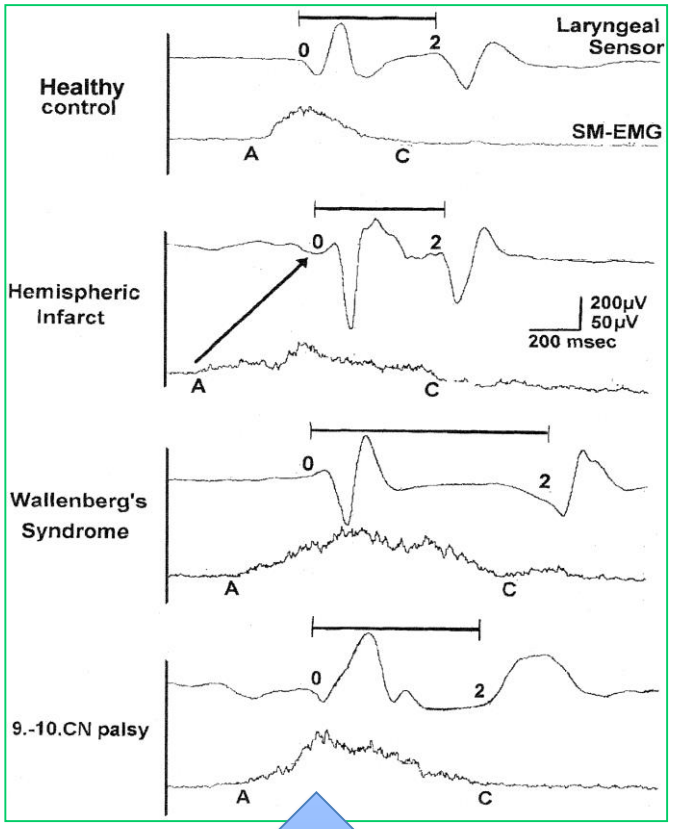
(Jean A, 1990)


Supramedullary imputs
NTS
Peripheral afferent imputs
XII
NA
V
VII
IX
X
C1-C3
To contralateral NA
Medulla oblungata
Pons
Cervical cord

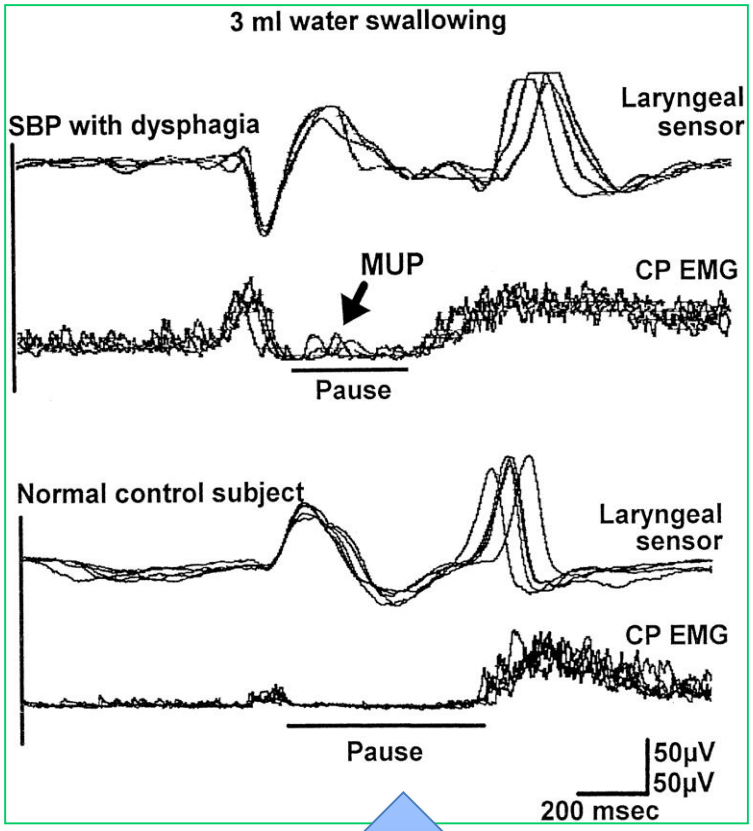

3 ml Water
Swallowing
Laryngeal Sensor
Orbicularis Oris
Masseter muscle
Submental
muscles
50 μV
30 μV
200 ms
70 μV
100 μV
50 μV
Thyroarytenoid
Cricopharyngeal
sphincter muscle


0
2
3 ml Water Swallowing
Laryngeal Sensor
Orbicularis Oris
Masseter muscle
Submental muscles
A
C
50 μV
30 μV
70 μV
100 μV
50 μV
200 ms
Thyroarytenoid
Cricopharyngeal sphincter muscle
CP EMG duration
Oral phase
Pharyngeal phase

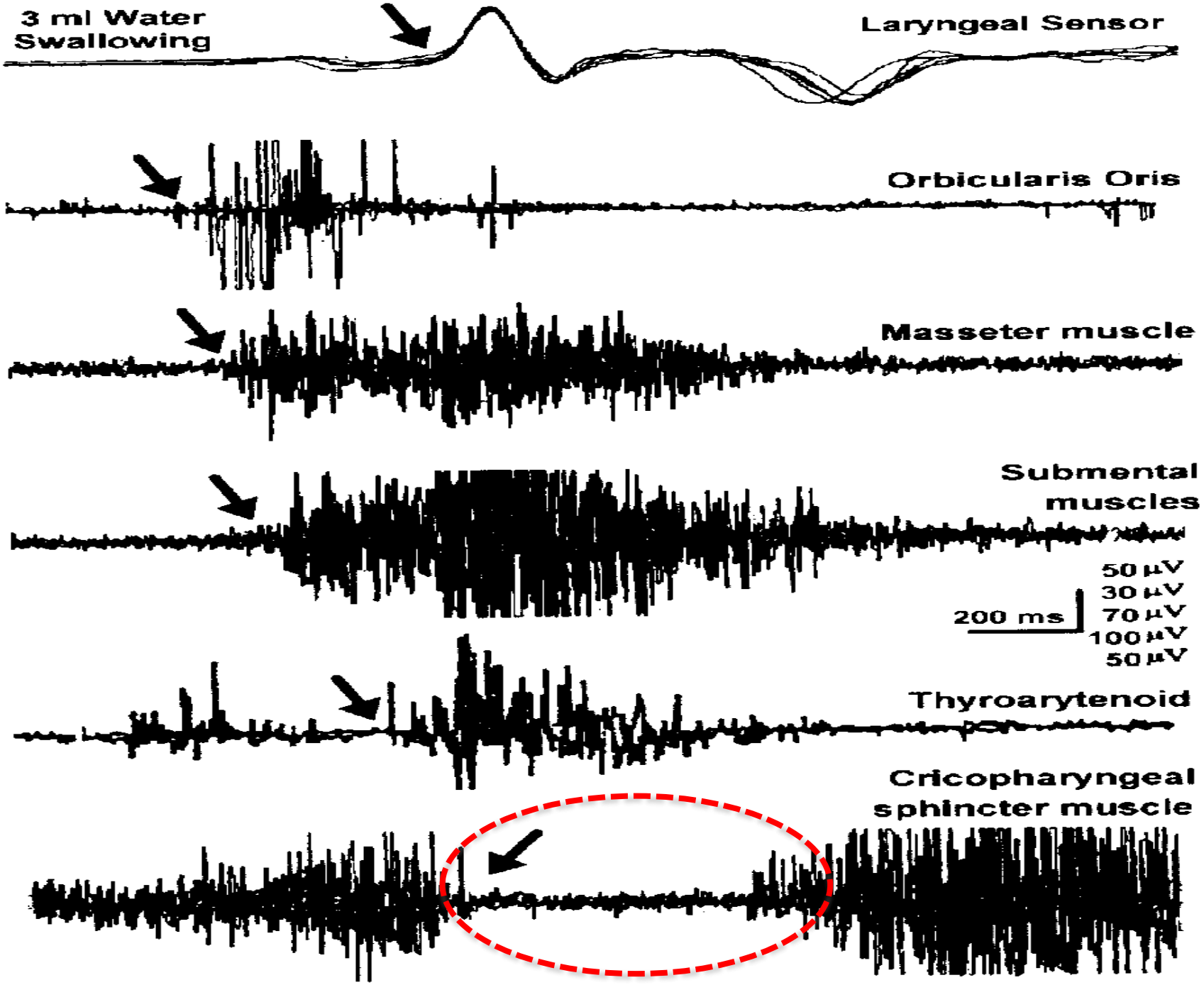
Stroke

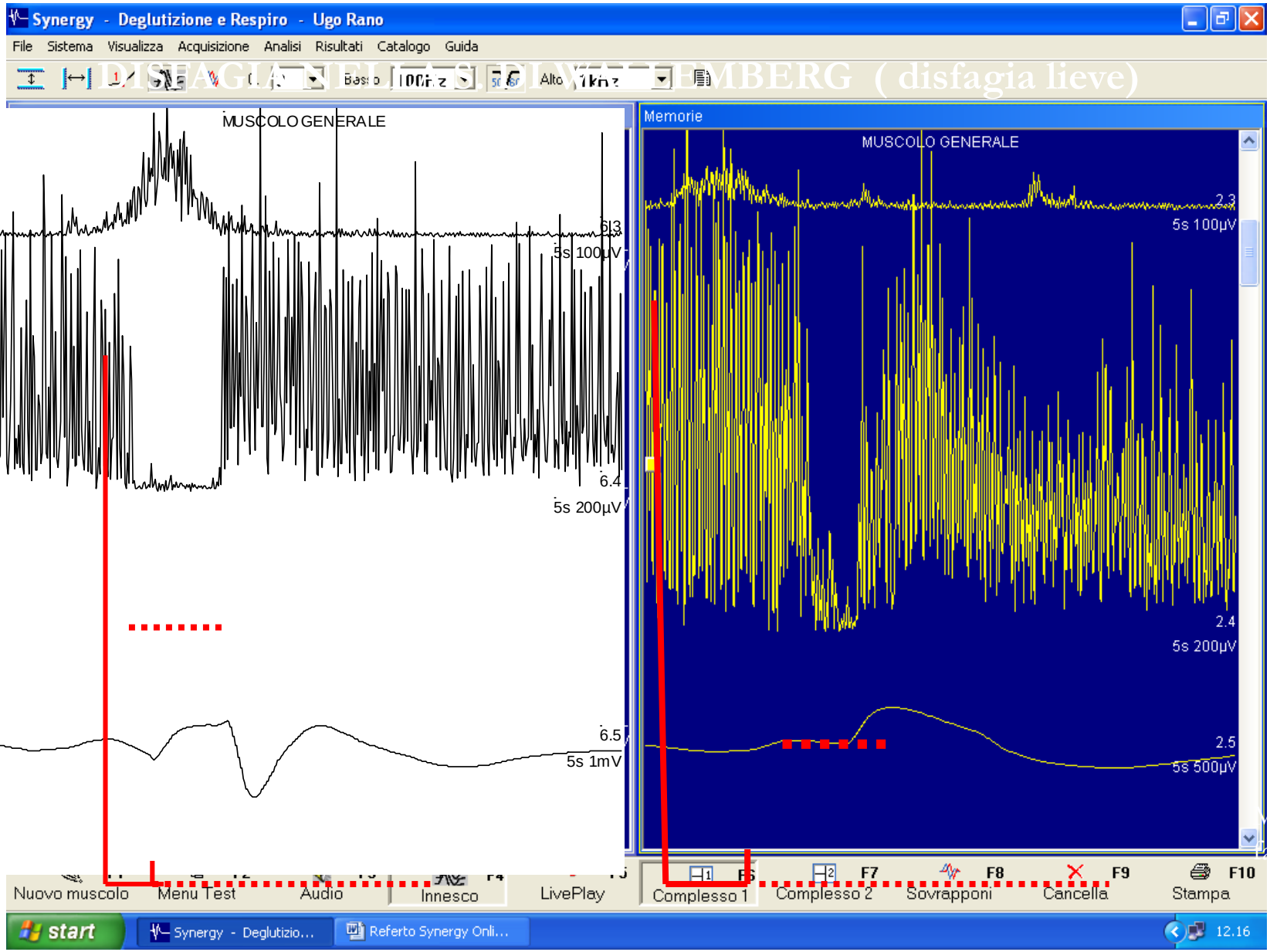


Oral phase involvement



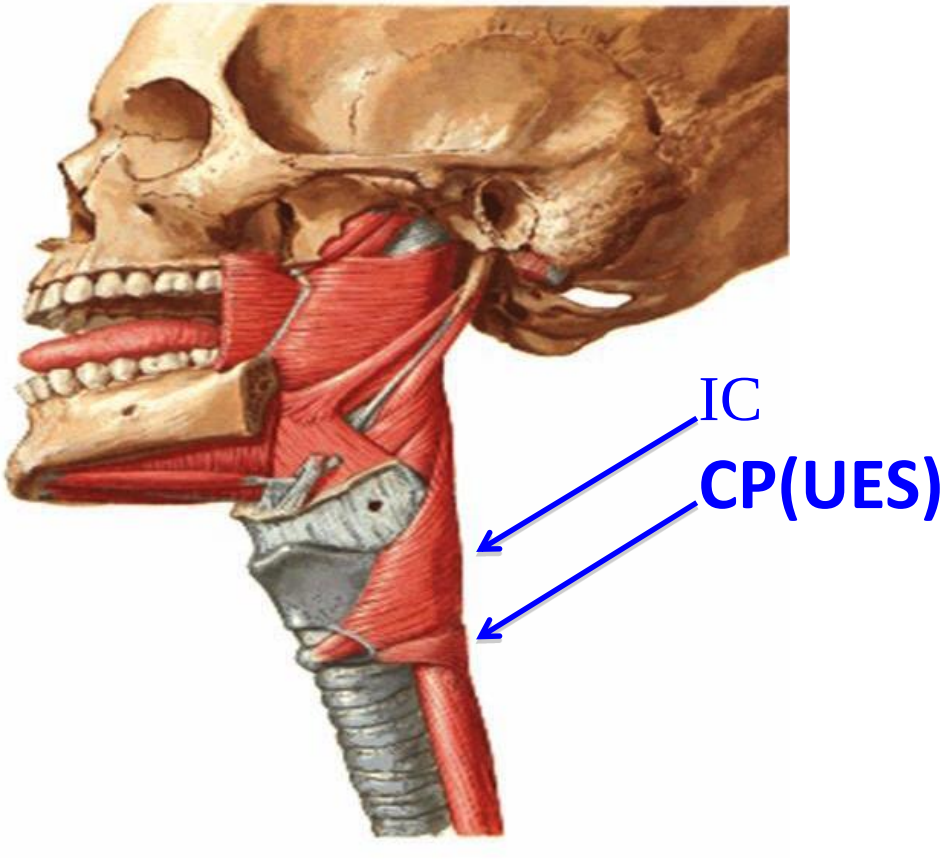
Pharyngeal phase involvement

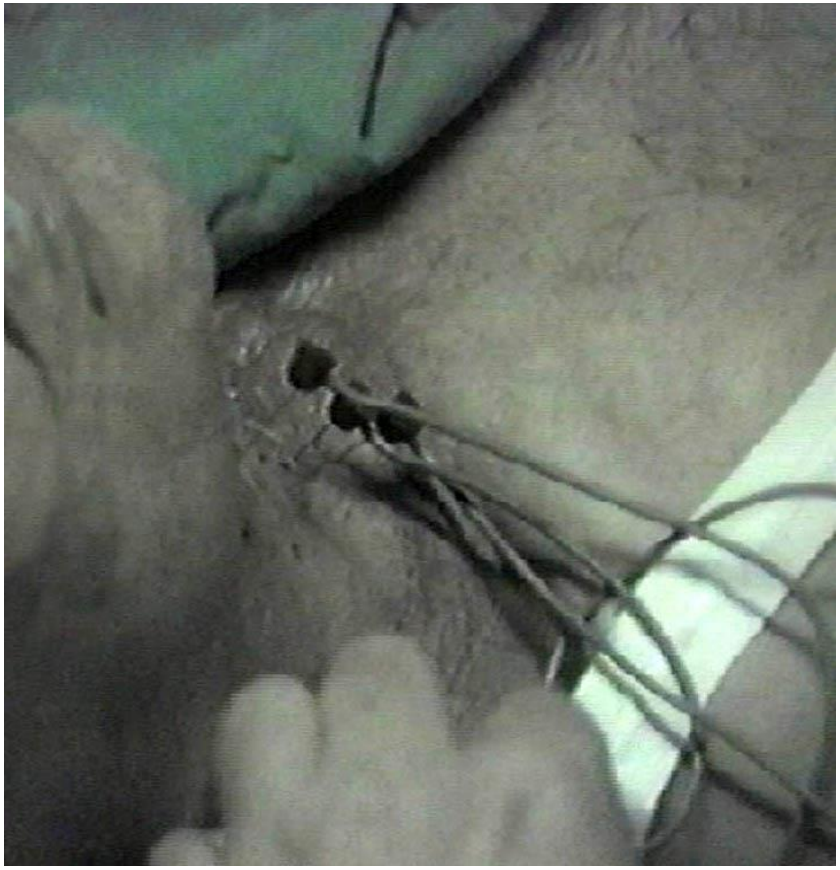

3 ml Water
Swallowing
Laryngeal Sensor
Orbicularis Oris
Masseter muscle
Submental
muscles
50 μV
30 μV
200 ms
70 μV
100 μV
50 μV
Thyroarytenoid
Cricopharyngeal
sphincter muscle



Courtesy of E. Alfonsi

Pharyngeal muscle evaluation: contemporary recordings from IC and CP muscles



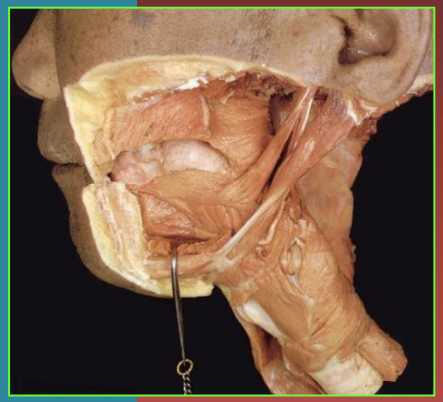


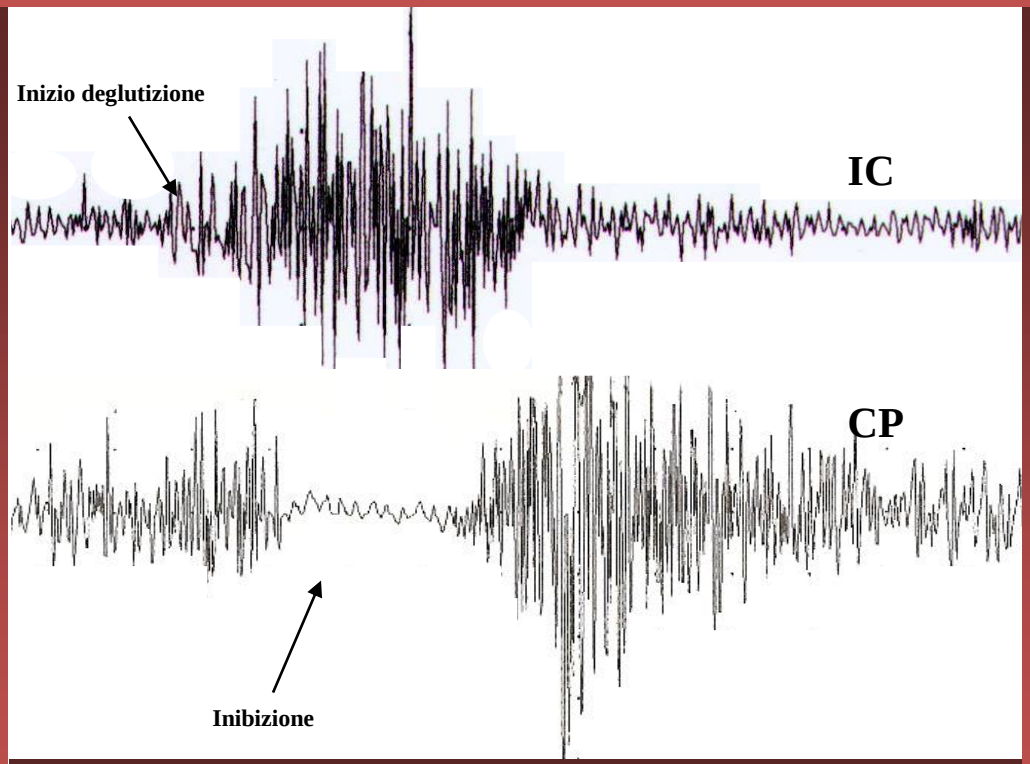
Restivo et al. Gastroenterology 2000; New Engl J Med 2002; J Neurol 2006; Eur J Neurol 2012; Neurology 2013

✓**EMG m. cricofaringeo (CP):** **ago introdotto 1.5 cm lateralmente al bordo esterno palpabile della cartilagine cricoidea in direzione postero-mediale.**
All' inserzione, a riposo: attività muscolare continua ad alta frequenza che scompare con l' atto del deglutire (pausa di circa 300-600ms)

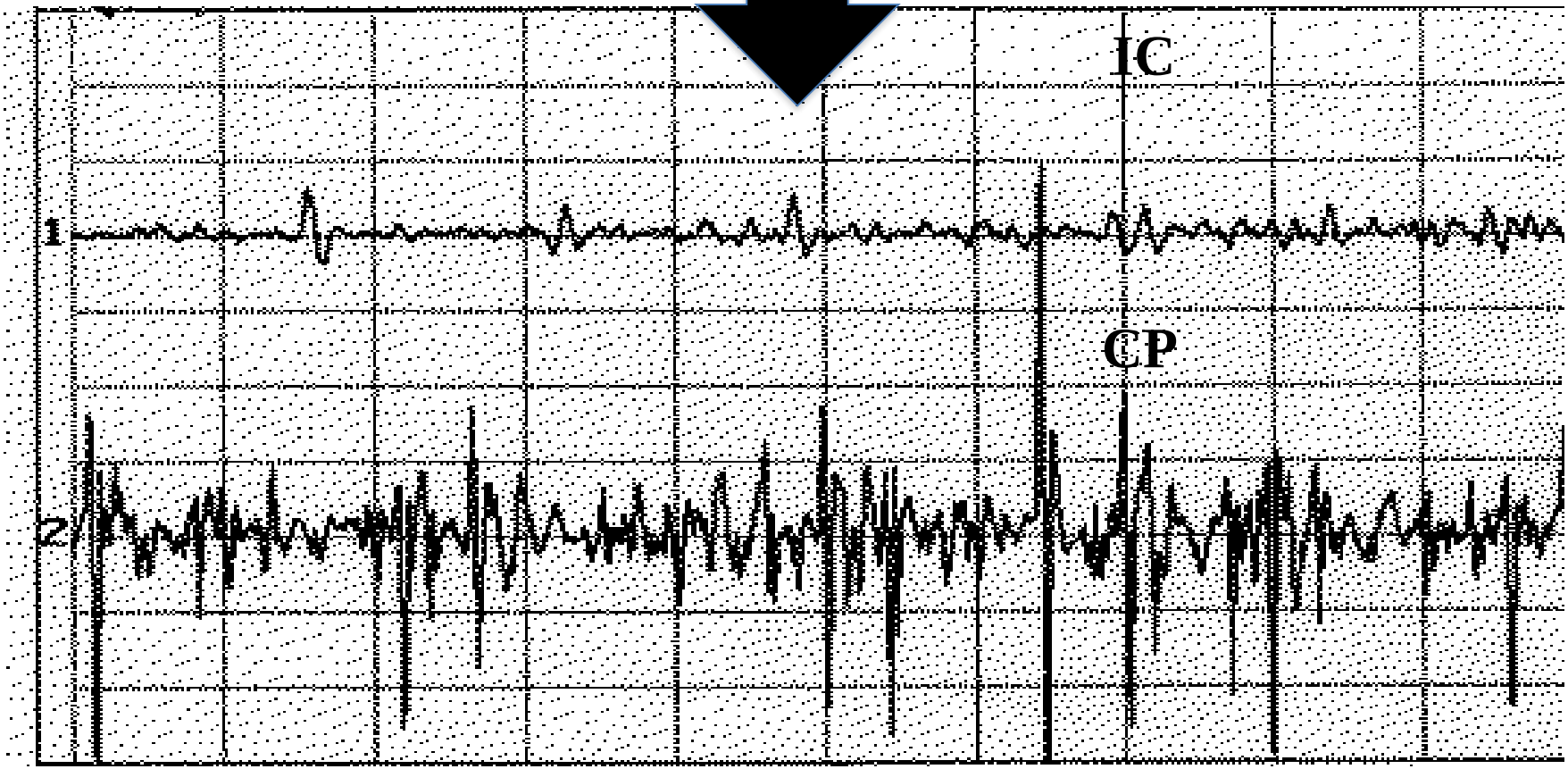
✓**EMG m. costrittore inferiore (IC):** **ago introdotto 3 cm sopra il sito di introduzione del CP, lateralmente al bordo laterale della cartilagine tiroidea.**
A riposo: nessuna attività. All' atto del deglutire attività da interferenza. Dopo la deglutizione scomparsa dell' attività volontaria

Simultaneous EMG recordings from IC e CP muscle





IC muscle reduced recruitment induces a reduced/absent CP muscle relaxation



SFINTERE ESOFAGEO SUPERIORE
PUNTI CHIAVE

•L a chiusura dello sfintere esofageo superiore (UES) include muscoli quali l'esofago cervicale, il cricofaringeo, il costrittore inferiore del faringe, ma soprattutto il muscolo cricofaringeo

•Le principali funzioni della chiusura dell'UES sono: 1) prevenire l'insufflazione di aria nell'esofago durante gli eventi caratterizzati da pressione intratoracica negativa, per esempio durante l'inspirazione., 2)prevenire il reflusso esofago-faringeo/laringeo durante la peristalsi esofagea

•Lo UES viene aperto in modo intermittente tramite il rilasciamento dei suoi muscoli sfinterici, mediante la contrazione dei suoi muscoli con funzione di stiramento del lume e mediante la spinta del bolo

•La funzione di apertura intermittente consente il flusso transfinterico di liquidi o gas durante eventi ortogradi, come la deglutizione o eventi retrogradi come , per esempio , il vomito

•L'apertura dell'UES prevede anteriormente la contrazione dei muscoli sopra-ioidei, ed infra-ioidei e , posteriormente, quella dei muscoli faringei superiori

•Le funzioni motorie e sensitive dell'UES sono controllate dai rami dei nervi vago e glossofaringeo

•Il nucleo ambiguo è il nucleo motore primario dello UES mentre il nucleo del tratto solitario è il sito primario di convergenza delle afferenze sensitive dello UES

•Le specifiche attività dei singoli muscoli dello UES dipendono dalle differenti funzioni a cui tale struttura è preposta: variazioni del tono , deglutizione, conati di vomito o vomito , eruttazione,

•Lo UES partecipa ad un elevato numero di riflessi del tratto digestivo che determinano in alcuni casi l'apertura in altri l'aumento di tono dello UES

Se i disturbi della deglutizione non si risolvono entro 6 mesi di terapia riabilitativa e/o medica è indicato il ricorso a *miotomia dello sfintere esofageo superiore*

McKenna and Dedo 1992

Miotomia Chirurgica

- **Invasiva**
- **Necessita di anestesia generale**
- **Non effettuabile in pazienti particolarmente defedati**
- **Effetti collaterali importanti**
- **Definitiva**

Botulinum toxin A for cricopharyngeal dystonia

SIR—We report the use of botulinum toxin A in a dysphagic patient with cricopharyngeal dystonia who had required a feeding gastrostomy for almost a year.

An active 86-year-old man who had had intermittent mild dysphagia for 12 years presented with complete dysphagia for solids and liquids and weight loss of 15 kg. Although earlier direct oesophagoscopy and barium swallow (at 74) had shown no evidence of a pharyngeal web or cricopharyngeal spasm, video-fluoroscopy now showed failure of any material to pass into the proximal oesophagus with puddling in the valleculae and pyriform sinus. A percutaneous endoscopic gastrostomy (PEG) feeding tube was inserted. He had had a permanent tracheostomy at 74 after several episodes of acute laryngeal stridor which had preceded the dysphagia. Laryngoscopy had shown apparent bilateral cord paresis in a paramedian position. At follow-up 5 months later he spoke fluently with occlusion of the tracheostomy and only complained of occasional dysphagia.

Review some months after PEG insertion elicited a several year history of occasional stiffening and cramping of the left hand such that he was unable to use if for periods of 20–30 s. A diagnosis of multifocal dystonia was made and subsequent multichannel electromyography (EMG) showed inappropriate activation of cord adductors with inspiration and no evidence of paralysis of the posterior crico-arytenoids, findings consistent with a diagnosis of laryngeal dystonia. EMG sampling of cricopharyngeus showed prominent tonic activity uninterrupted by swallow, consistent with dystonia. EMG-guided botulinum toxin (Botox with Allergan, 16 IU total, 8 IU each side) was injected into cricopharyngeus; a curved needle under fluoroscopic control. 6 h after the injection the patient realised that he was swallowing chocolate that he habitually chewed and needed to spit out. Within a few days he was able to cope with virtually all foods, and a follow-up video fluoroscopy 2 weeks post-injection confirmed striking functional recovery.

The possibility of laryngeal dystonia was only fully appreciated following the publication of a report[1] that showed that stridor can be due to a focal laryngeal dystonia, in some cases as part of a multifocal dystonia.

John Dunne, Michael Hayes, David Cameron

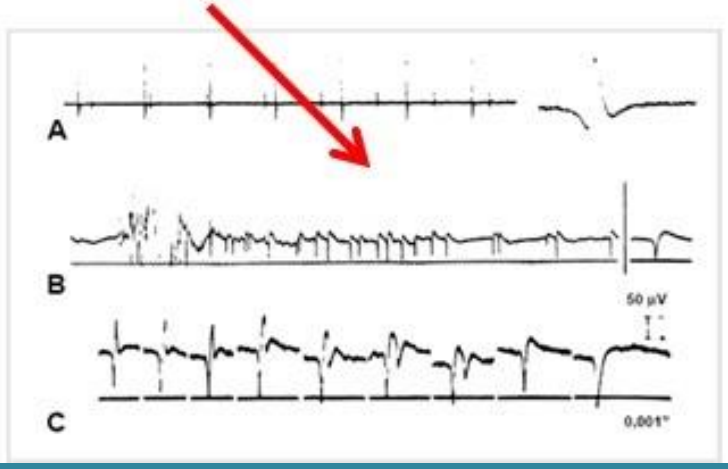
Department of Neurology, Department of Radiology, Royal Perth Hospital, Perth 6001, Western Australia

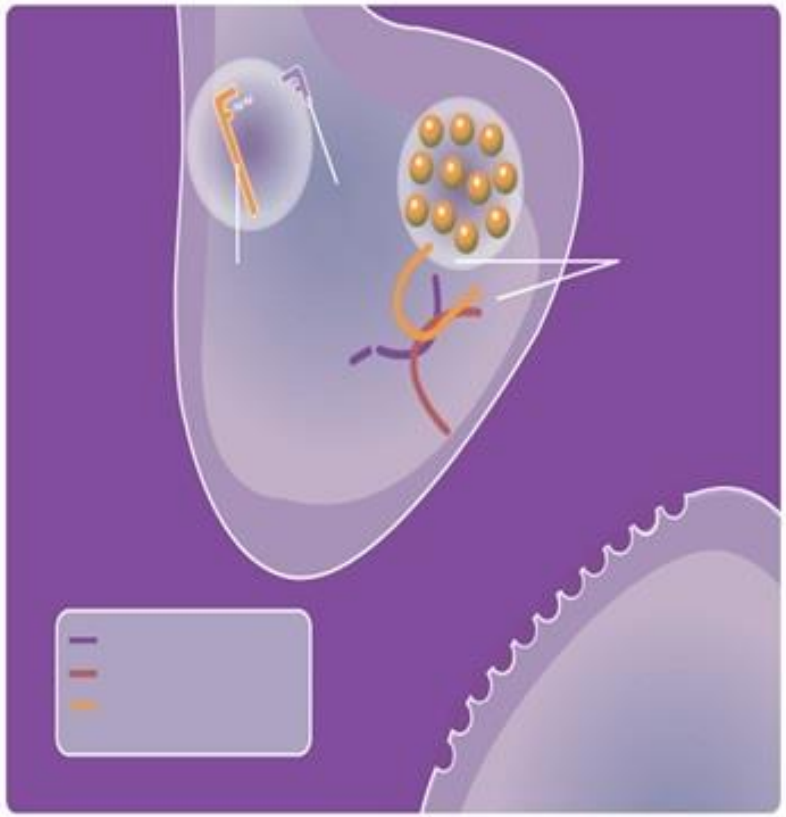
1 Marian M-H, Klap P, Perrin A, Cohen M. Stridor and focal laryngeal dystonia. *Lancet* 1992; **339**: 457–58.

Chemical Denervation

When BTX type A reaches the inside of the nerve terminal it acts by the SNAP-25 cleavage.

The formation of the SNARE complex is imperfect, and interferes with the cholinergic vesicle exocytosis and causes chemical denervation



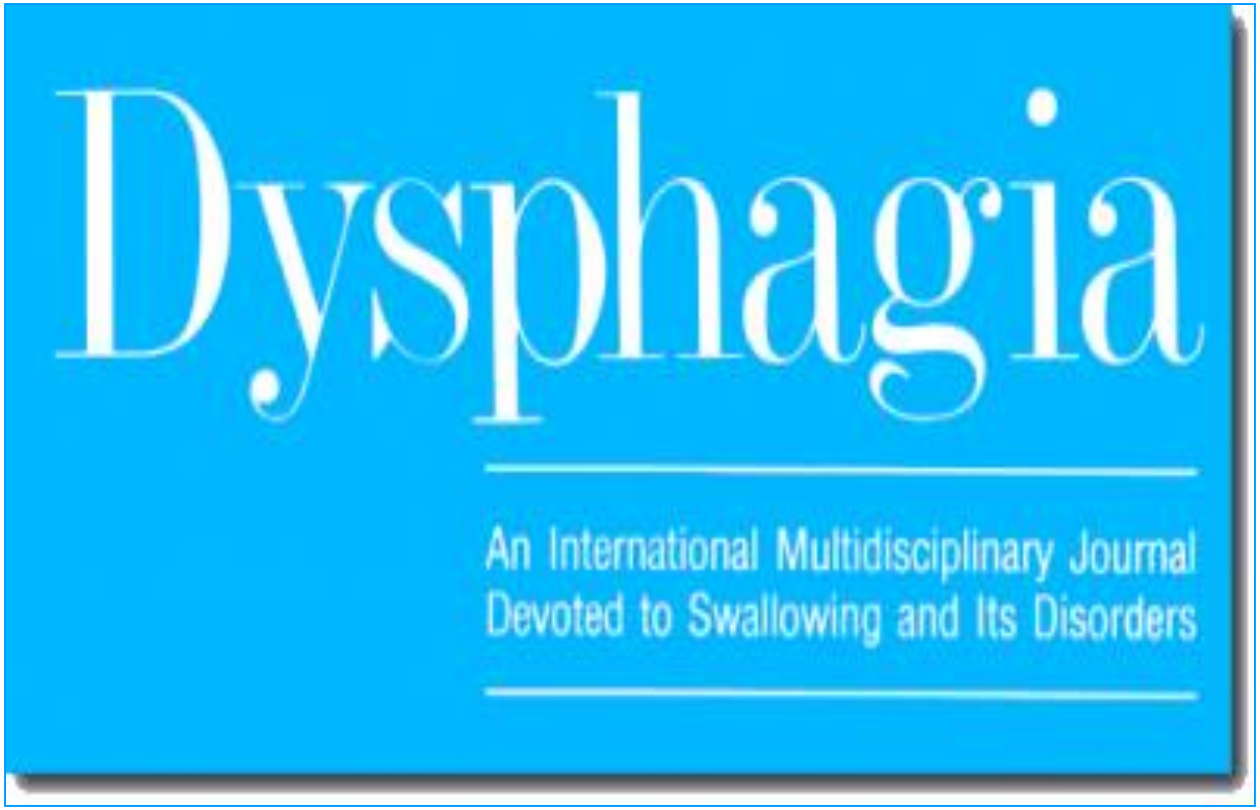


Gastroenterology

Successful Botulinum Toxin Treatment of Dysphagia in Oculopharyngeal Muscular Dystrophy

DOMENICO A. RESTIVO, ROSARIO MARCHESE RAGONA, ALBERTO STAFFIERI, and DOMENICO DE GRANDIS

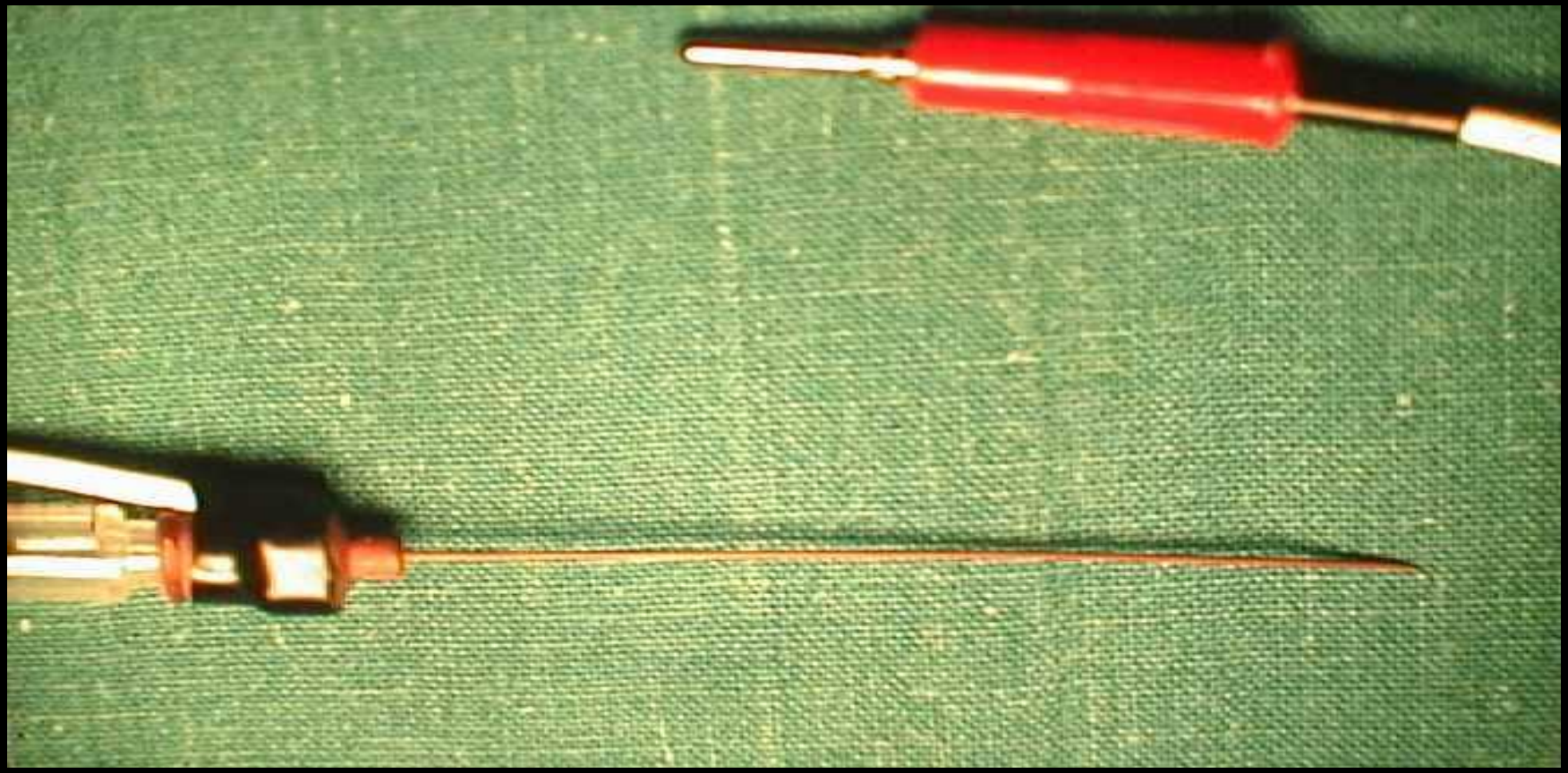
Gastroenterology 2000 119: 1416



BOTULINUM TOXIN TREATMENT OF DYSPHAGIA IN A YOUNG CHILD WITH NEMALINE MYOPATHY

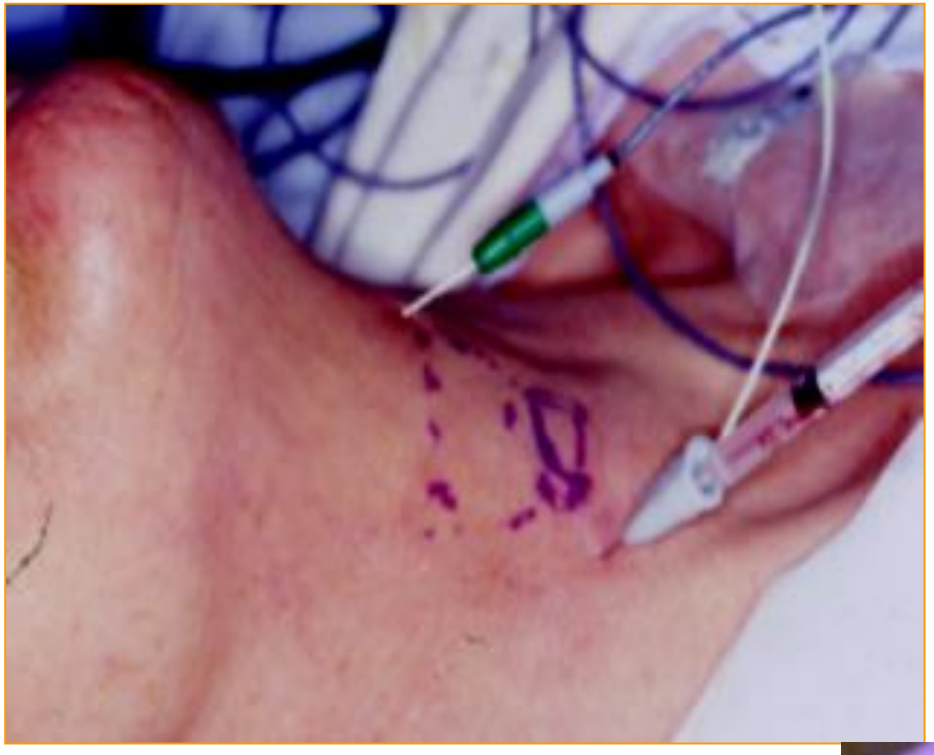
Restivo DA, Marchese-Ragona R, Giuffrida S, Falsaperla R

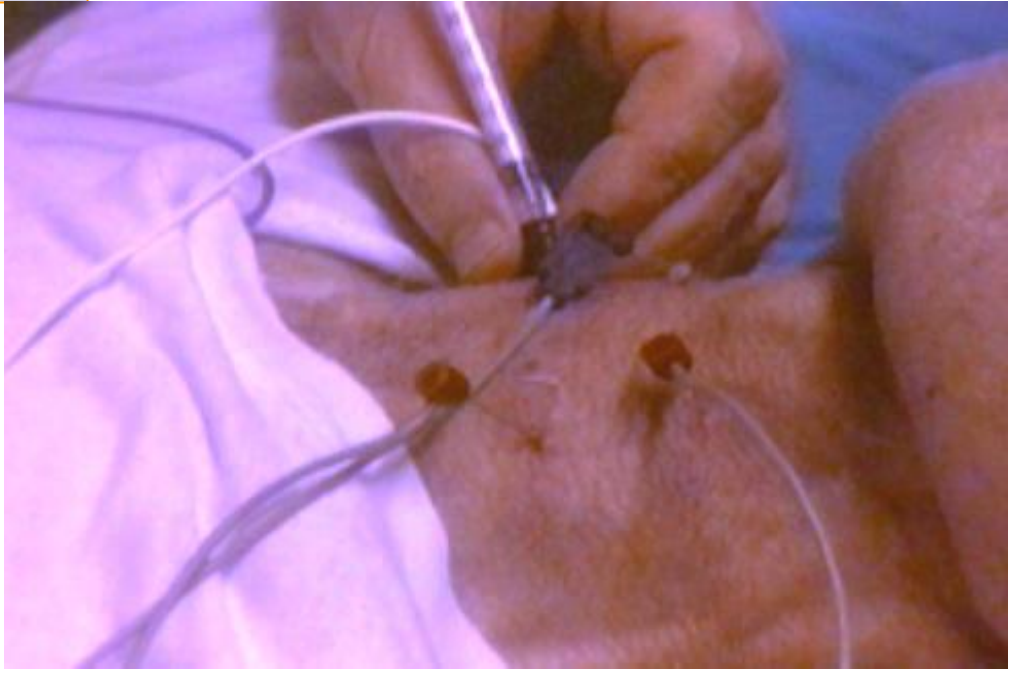
Dysphagia 2001



Inoculazione del UES sotto ctrl EMG

Botox: 5-15 UI per lato
Dysport: 15-50 UI per lato
Xeomin 5-15 UI per lato

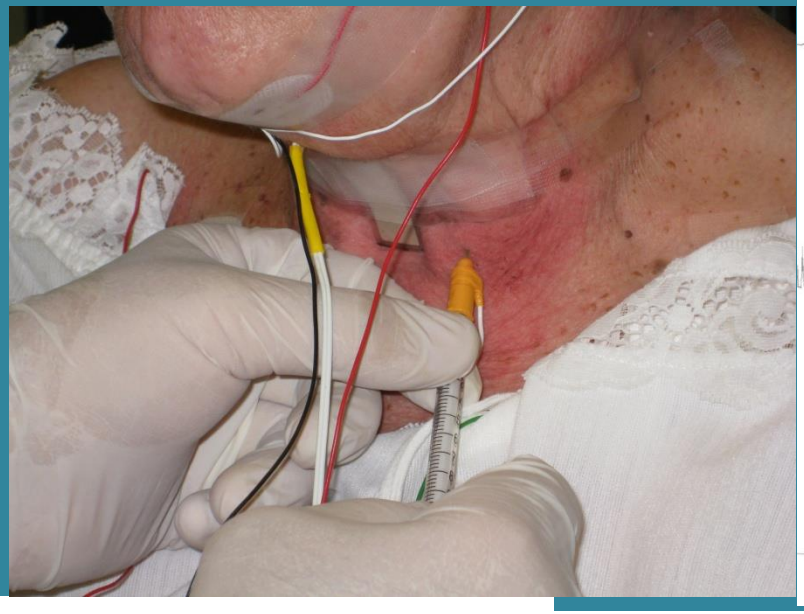


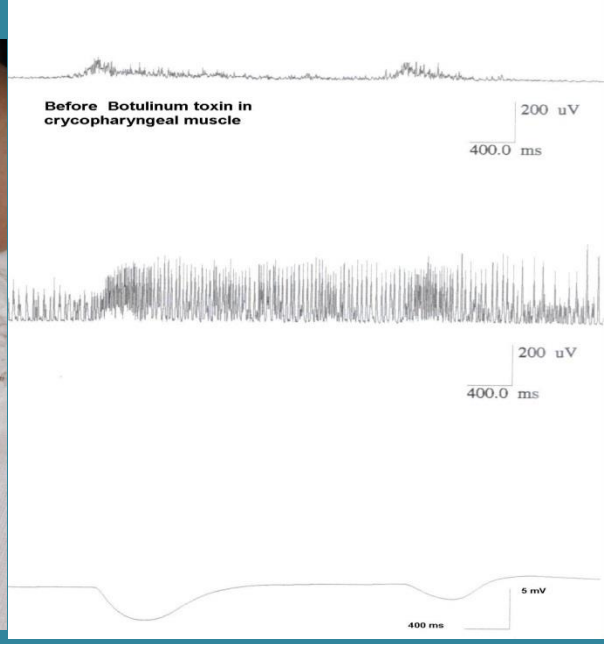


Xeomin or BOTOX:15 U

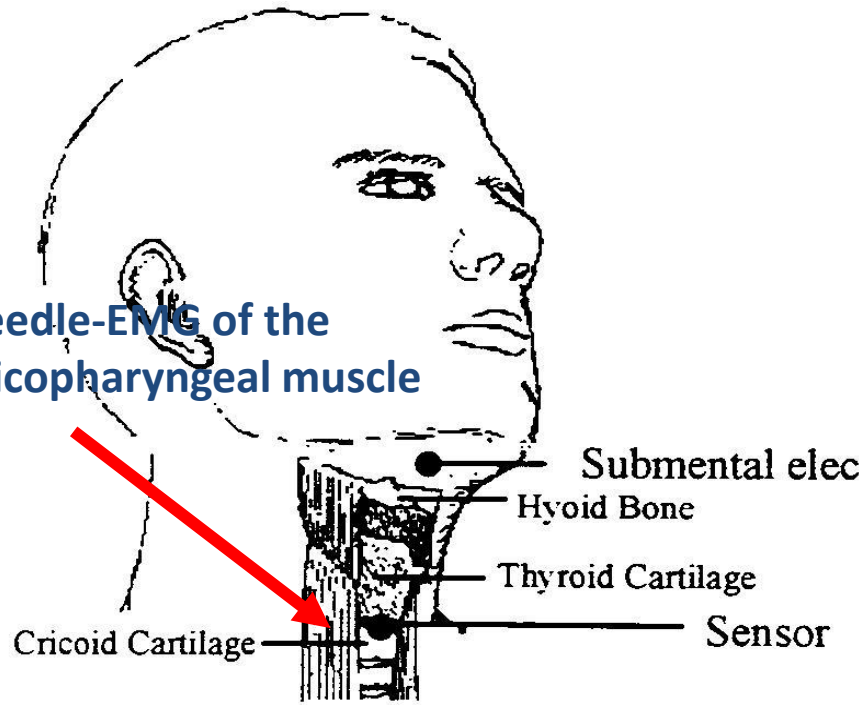
Dysport: 50-60 U

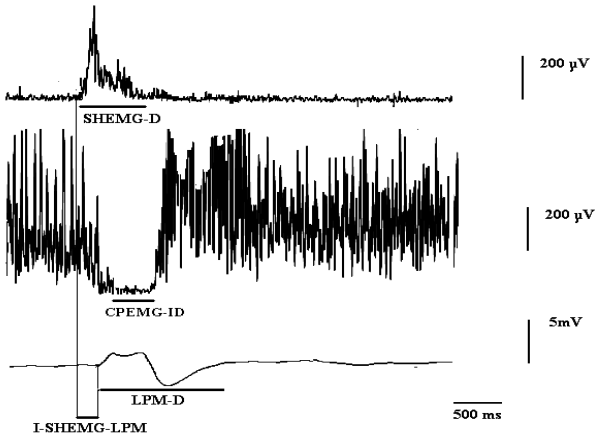
(unilateral injection)





Needle-EMG of the Cricopharyngeal muscle



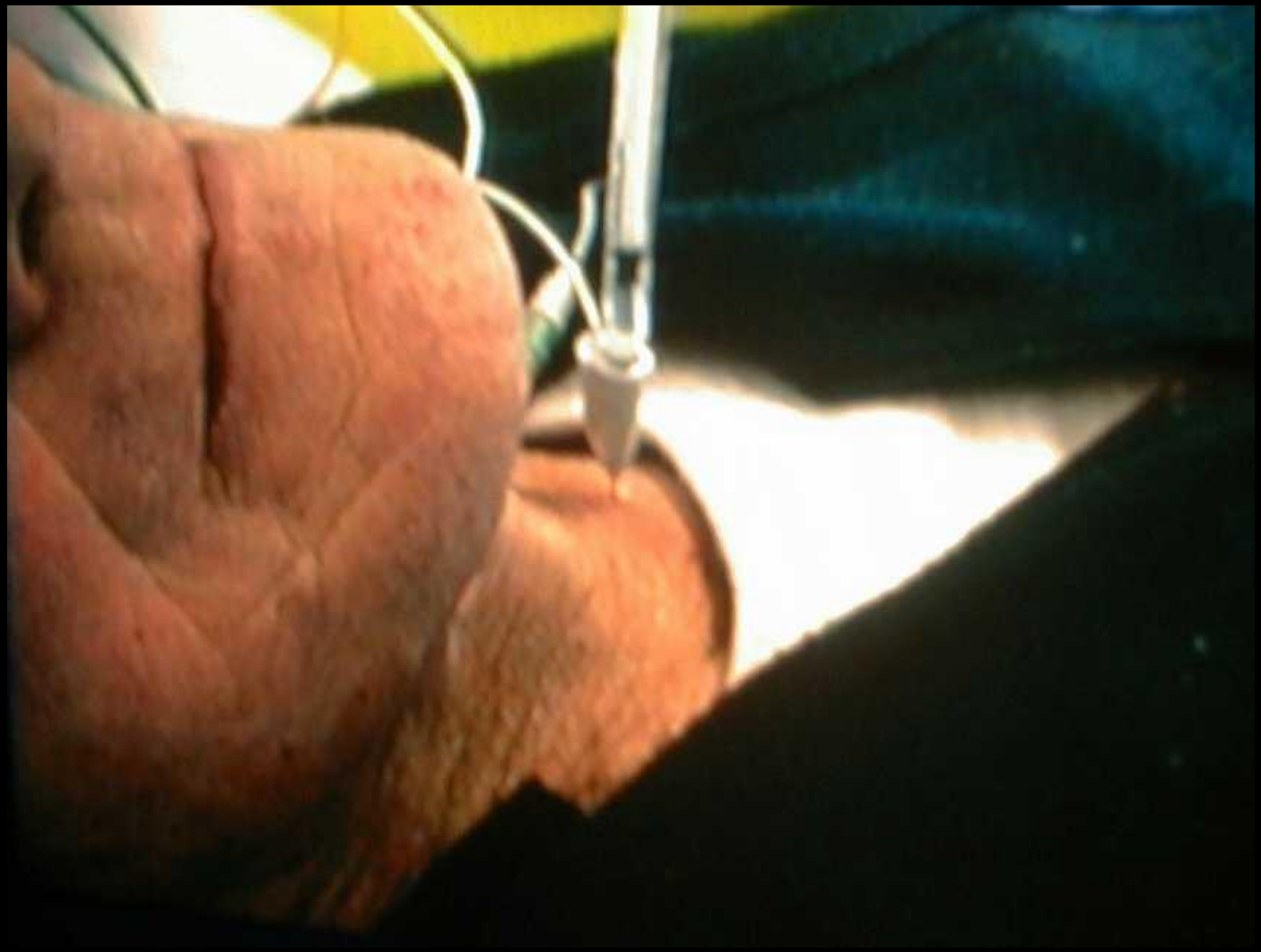


An electrophysiological approach to the diagnosis of neurogenic dysphagia: implications for botulinum toxin treatment

E Alfonsi, I M Merlo, M Ponzio, et al.

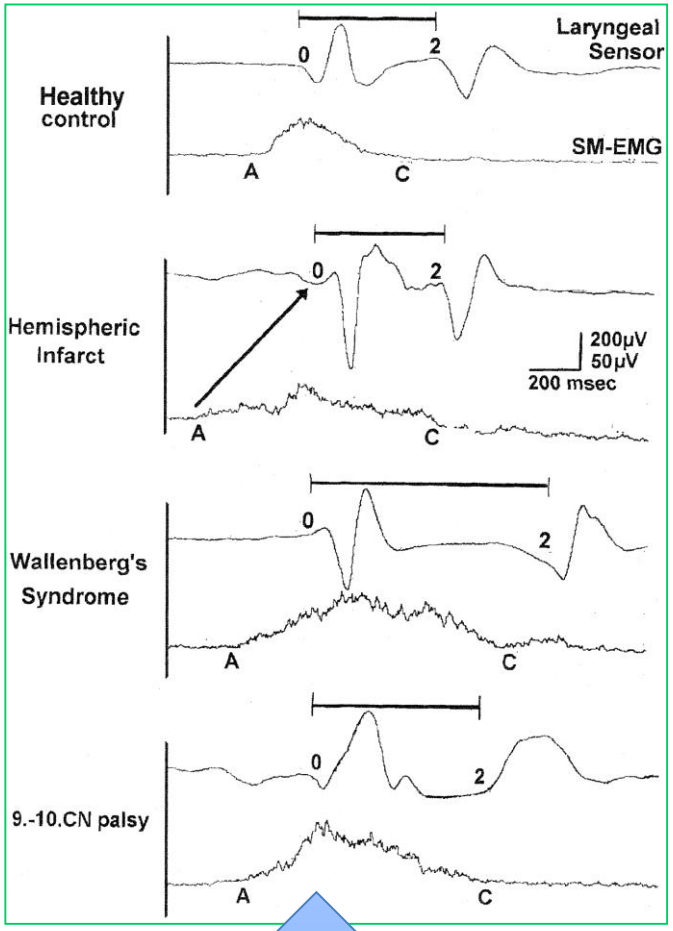
J Neurol Neurosurg Psychiatry 2010 81: 54-60 originally published online September 16, 2009

Quali pazienti trattare ?



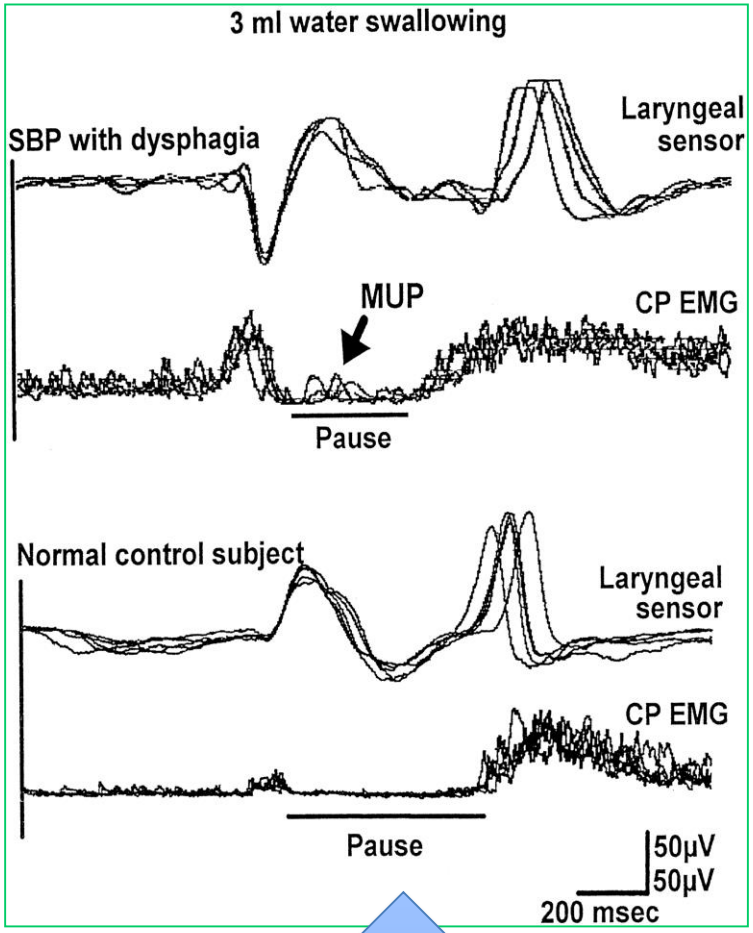
Non tutti i pz con DN; solo quelli con ipertono del UES

NO

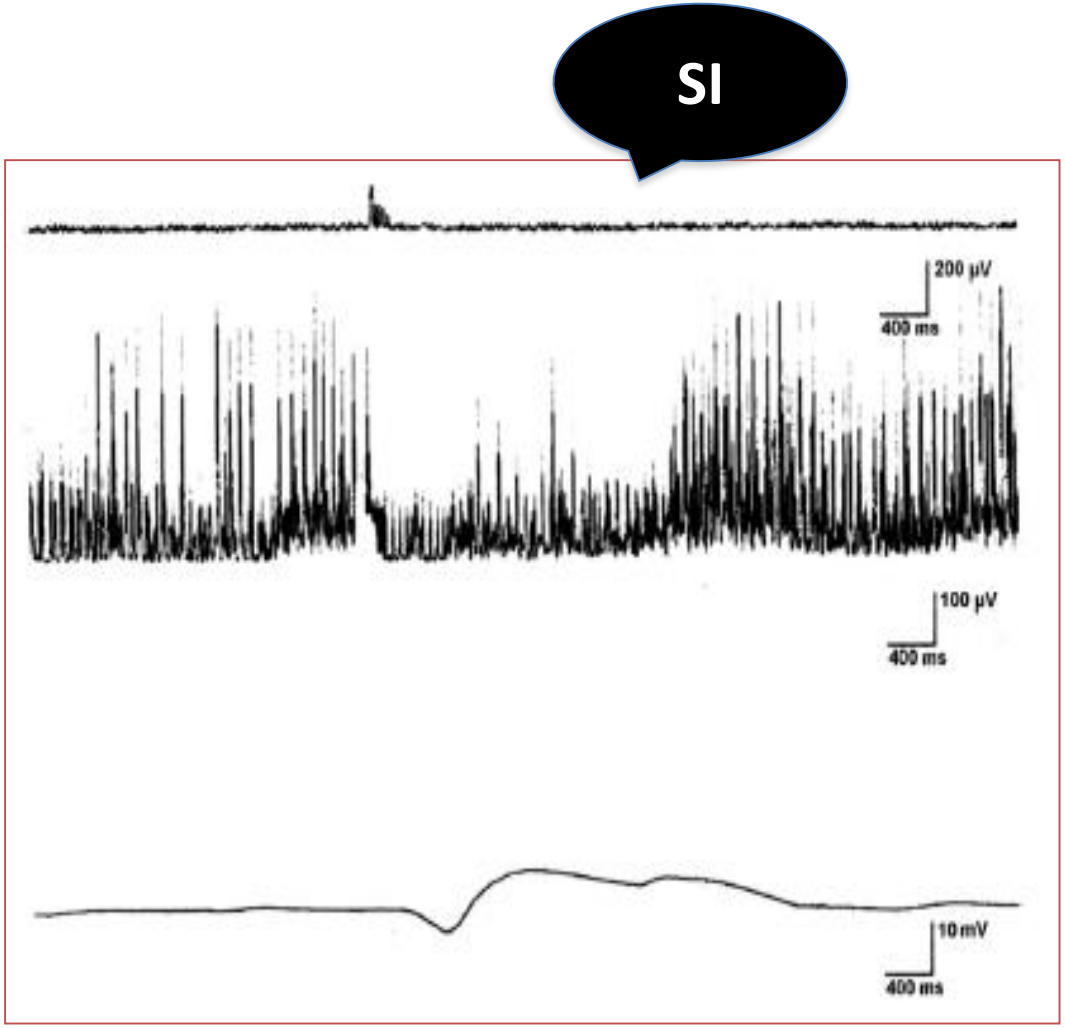


Oral phase involvement

SI



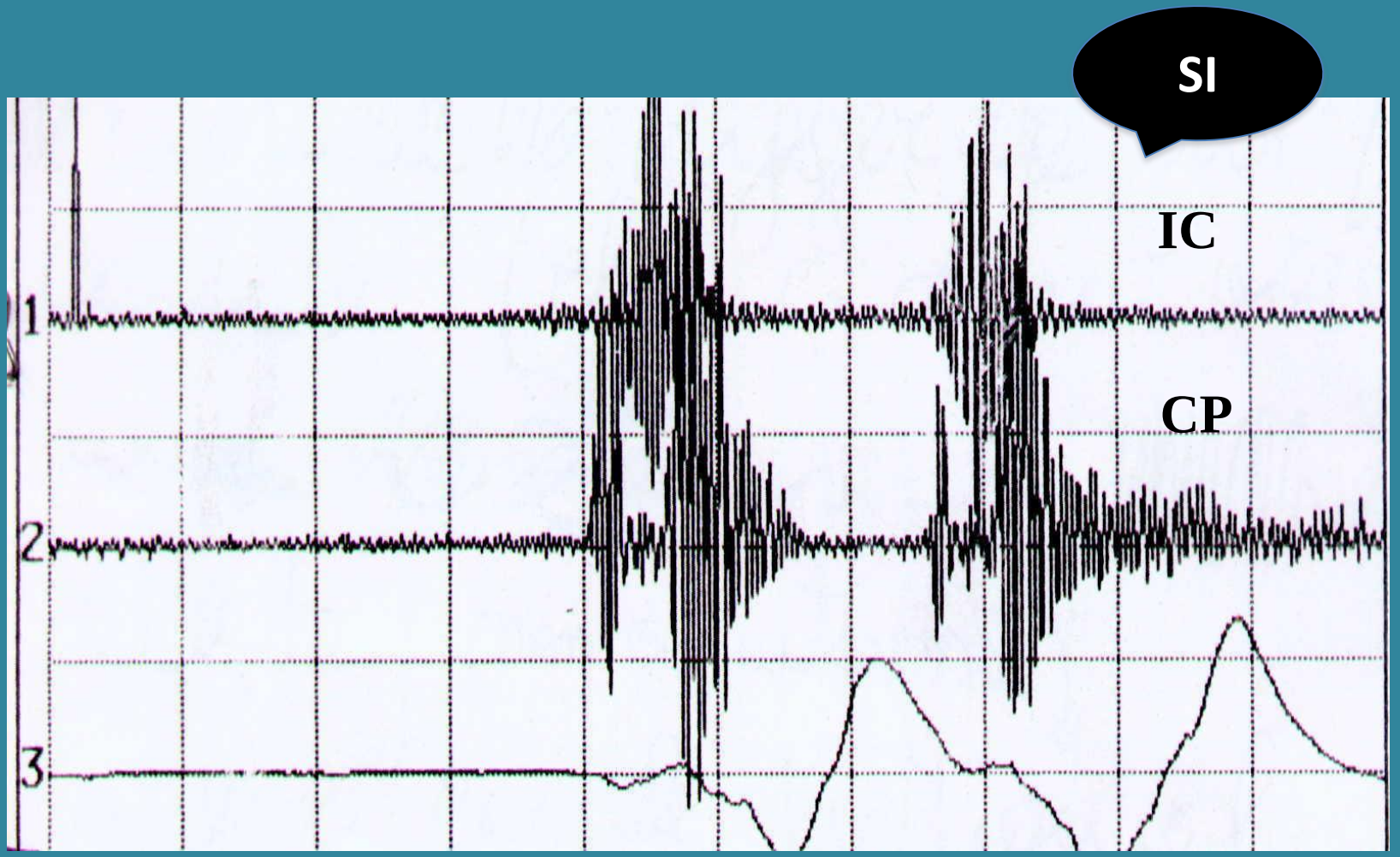
Pharyngeal phase involvement



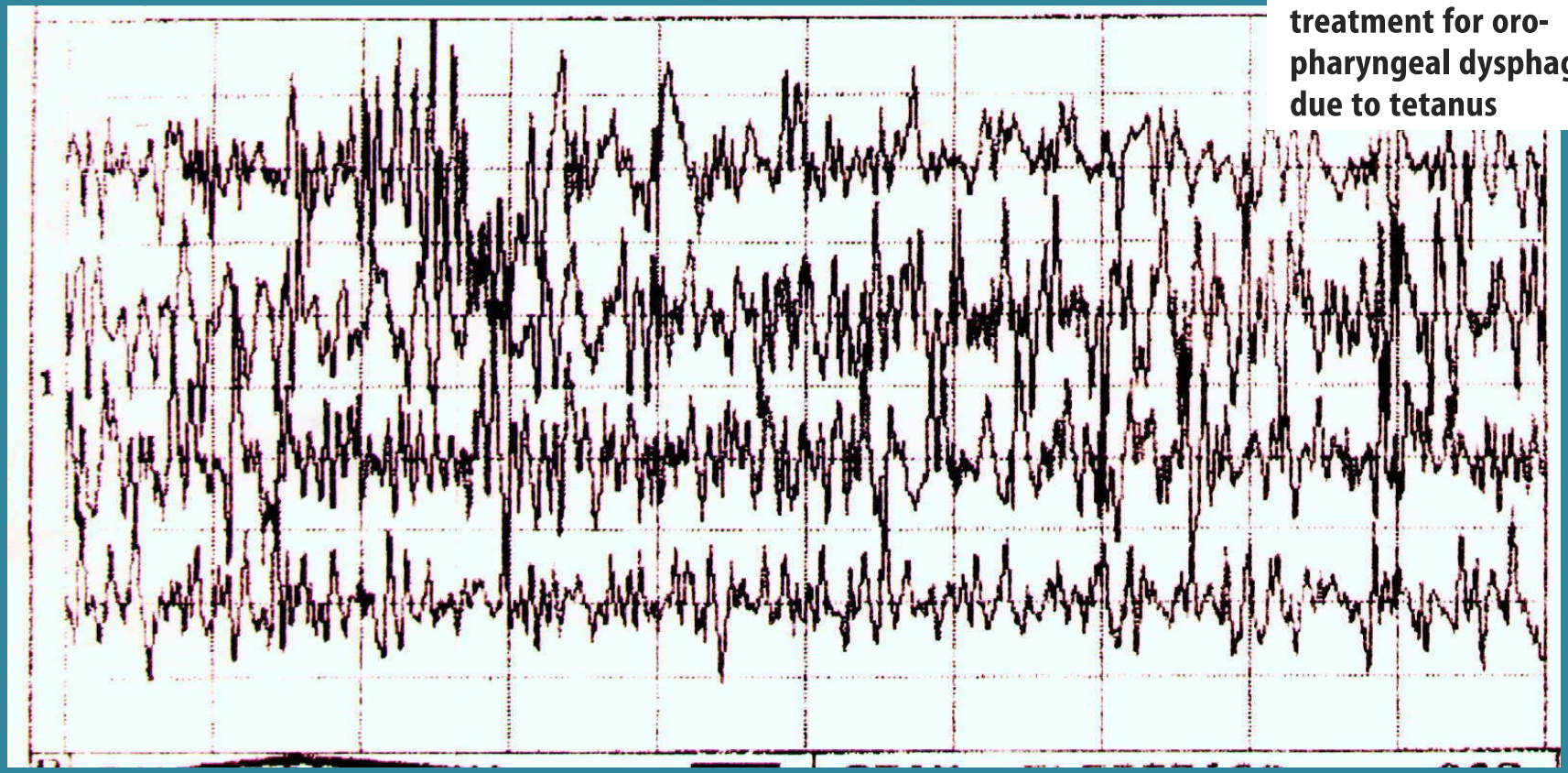
PSP

Alfonsi et al., 2007

PD: Pharyngeal muscle dyscoordination



Tetanus

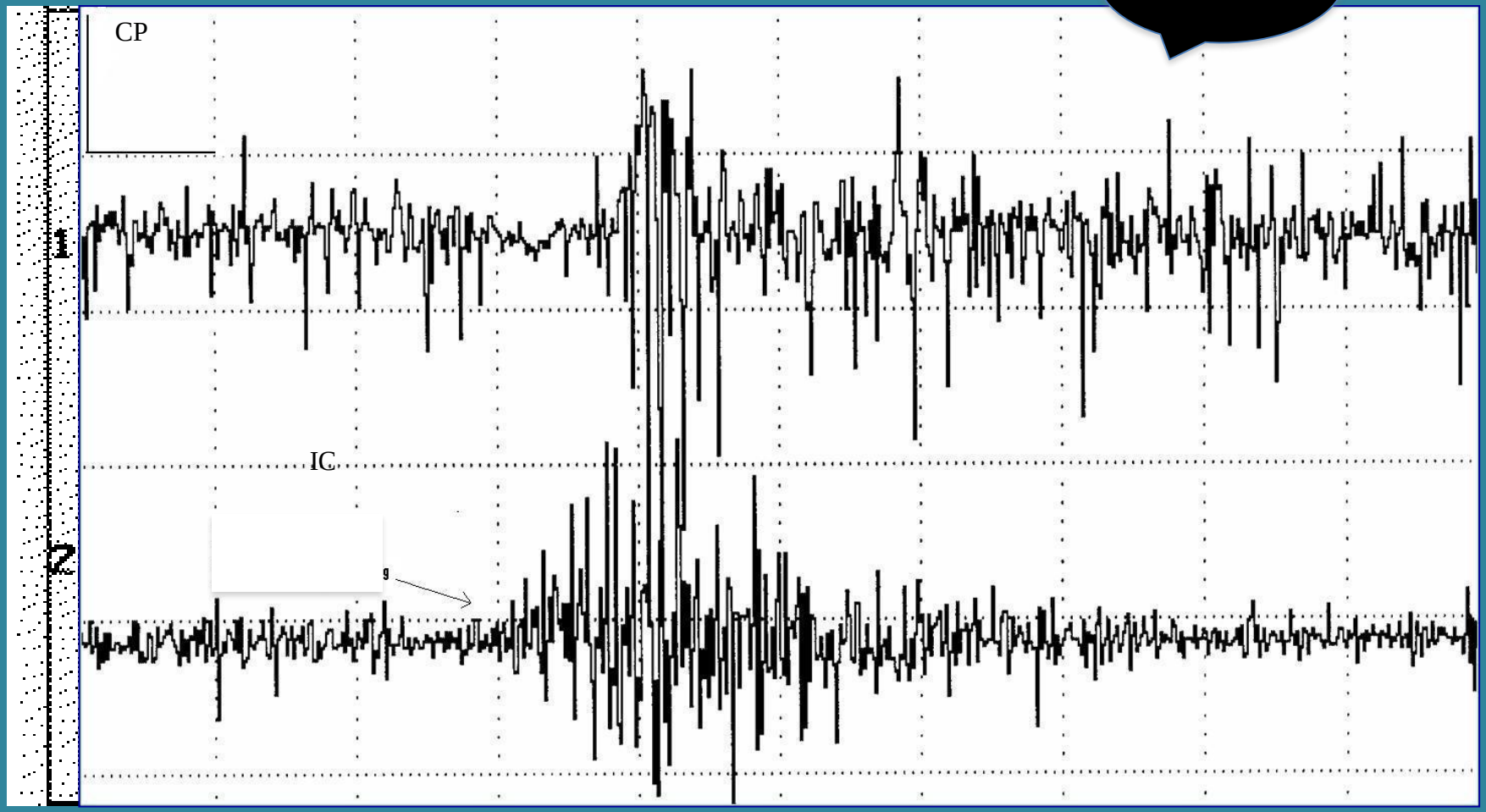


J Neurol (2006) 253 : 388–389
DOI 10.1007/s00415-005-0975-9

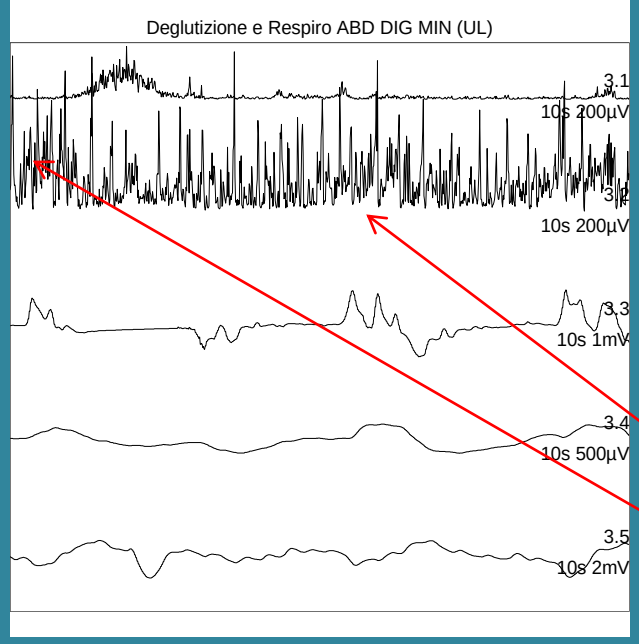
Domenico A. Restivo
Rosario Marchese-Ragona

Botulinum toxin treatment for oro-pharyngeal dysphagia due to tetanus

SI

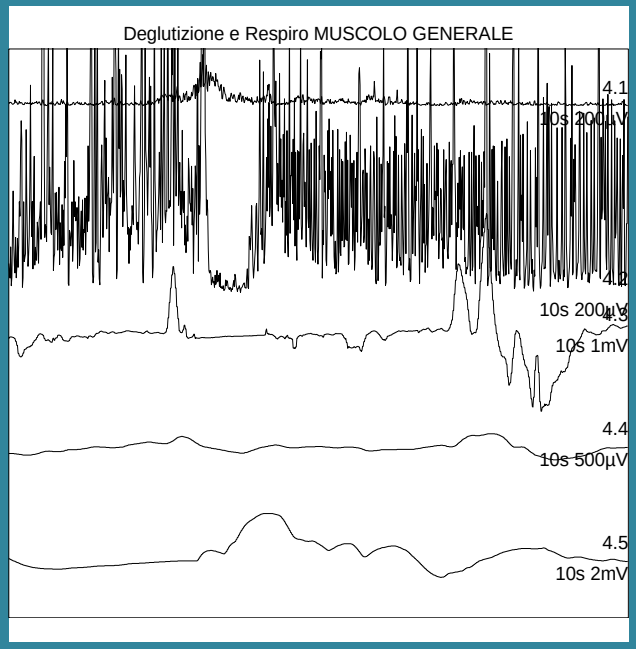


Dysphagia in Wallenberg syndrome caused by vertebral artery dissection



16 weeks after the onset of the disease. Inoculation of BTX into the CP muscle (15 U of Xeomin or Dysport 50-60 U or BOTOX 15 U)

Pseudorhythmic myoclonic bursts overlapping baseline tonic activity of the CP muscle



12 weeks after BTX injection

Courtesy of E. Alfonsi

The NEW ENGLAND JOURNAL of MEDICINE

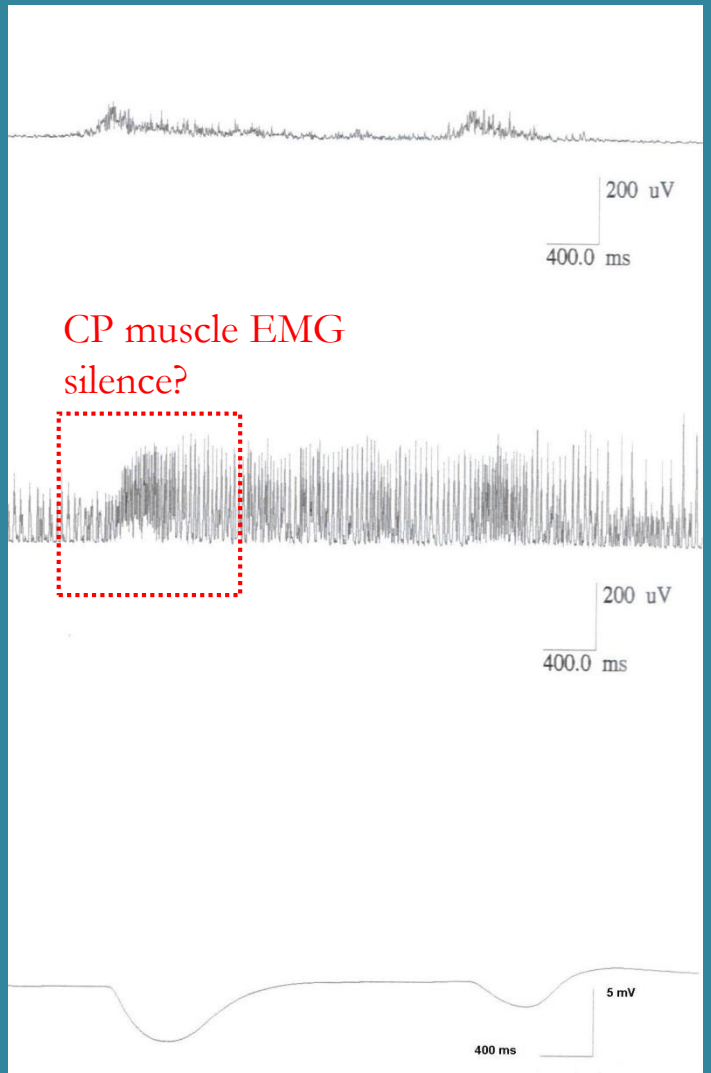
Botulinum toxin treatment for cricopharyngeal dysfunction in Parkinson's Disease

Restivo DA, Palmeri A, Marchese-Ragona R

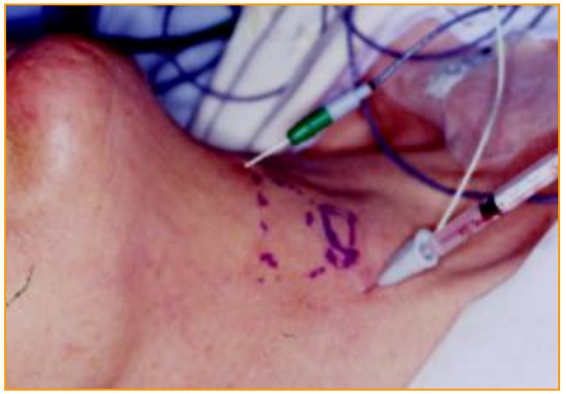
N Engl J Med 2002, 346, 1174-1175

Dysphagia in Parkinson Disease

Only PD patients with severe dysphagia and the highest UPDRS scores show a reduced or absent EMG inhibition of the cricopharyngeal muscle



Alfonsi et al. .'Electrophysiological study of oral-pharyngeal swallowing in Parkinsonian Syndromes'
Neurology , 2007, 68: 583-590



Botulinum toxin improves dysphagia associated with multiple sclerosis

Restivo DA, Marchese-Ragona R, Patti F, Solaro C, Maimone D, Zappalà G, Pavone A
Eur J Neurol 2011; 18(3): 486-490

ALS dysphagia pathophysiology

Differential botulinum toxin response

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ABSTRACT

Objectives: This study looked at the effect of botulinum toxin type A (BoTox-A) in patients with amyotrophic lateral sclerosis (ALS) with dysphagia due to isolated upper motor neuron (UMN) involvement or combined UMN/lower motor neuron (LMN) impairment associated with oral phase or oropharyngeal muscles involvement. Establishing whether different pathophysiologic mechanisms underlie different responses to BoTox-A treatment may have important implications for patient management.

Patients and methods: We screened 35 patients with sporadic ALS with dysphagia and included in the study 20 out of 35 with upper esophageal sphincter (UES) hyperactivity. We divided these 20 patients into 2 groups, based on the presence or absence of LMN impairment. Irrespective of the groups, we treated all 20 patients with BoTox-A injected into the UES. The study outcome was dysphagia severity scored using the Penetration/Aspiration Scale (PAS), measured before and 2, 4, and 20 weeks after injection.

Results: Significant mean PAS reduction was noted at weeks 2 and 4. The botulinum-dependent PAS reduction was entirely associated with the variability shown by the group of patients with no sign of LMN impairment (group 2) and was not observed in group 1.

Conclusions: The significant improvement observed in patients with isolated UES dysfunction suggests that a different pathophysiology of ALS dysphagia predisposes patients to a different response to treatment with BoTox-A. This treatment may represent an alternative treatment to percutaneous endoscopic gastrostomy (PEG) or prolong PEG-free time.

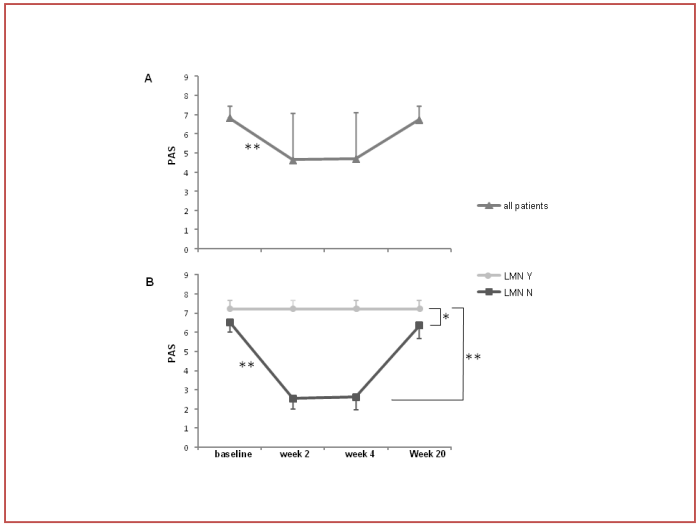
Classification of evidence: This study provides Class III evidence that botulinum is more effective at 2 and 4 weeks in improving dysphagia in patients with ALS with UES hyperactivity without LMN involvement (vs those with LMN involvement). *Neurology*® 2013;80:616–620

GLOSSARY

ALS = amyotrophic lateral sclerosis; **BoTox-A** = botulinum toxin type A; **CP** = cricopharyngeal; **IC** = inferior constrictor; **LMN** = lower motor neuron; **MS** = multiple sclerosis; **PAS** = Penetration/Aspiration Scale; **PD** = Parkinson disease; **PEG** = percutaneous endoscopic gastrostomy; **UES** = upper esophageal sphincter; **UMN** = upper motor neuron.

Table Clinical data of 20 patients with ALS with dysphagia due to UES hyperactivity

Age, y	Sex	Disease duration, y	Dysphagia duration, mo	PAS (baseline)	PAS (week 2)	PAS (week 4)	PAS (week 20)	LMN signs	Oral phase involvement	Fibrillation potentials
71	M	3	24	8	8	8	8	Y	Y	Y (S/S)
56	M	2.9	13.2	8	8	8	8	Y	Y	Y (S/S + IC)
66	F	1.8	7	7	7	7	7	N	Y	N
64	M	3.8	24.3	7	7	7	7	Y	Y	Y (IC)
70	M	4.3	31	7	7	7	7	Y	Y	Y (S/S)
65	M	2.1	12	7	7	7	7	N	Y	N
53	F	4	33	7	7	7	7	Y	Y	Y (IC)
63	F	3.2	29	7	7	7	7	Y	Y	Y (S/S)
56	M	2.6	17.3	7	7	7	7	Y	Y	Y (S/S + IC)
48	F	3.3	24	7	3	3	7	N	N	N
57	M	2.2	11	7	3	3	7	N	N	N
47	M	1.7	7	7	3	3	7	N	N	N
62	M	1	5	7	3	3	7	N	N	N
54	M	1.6	9.2	7	3	4	7	N	N	N
69	F	2.1	11.1	7	2	2	6	N	N	N
64	M	2.6	18	6	2	2	6	N	N	N
66	M	3.1	35	6	2	2	6	N	N	N
54	M	2.9	29	6	2	2	6	N	N	N
56	F	3.9	27	6	2	2	6	N	N	N
55	M	3.7	36.3	6	3	3	5	N	N	N



Restivo et al., 2013

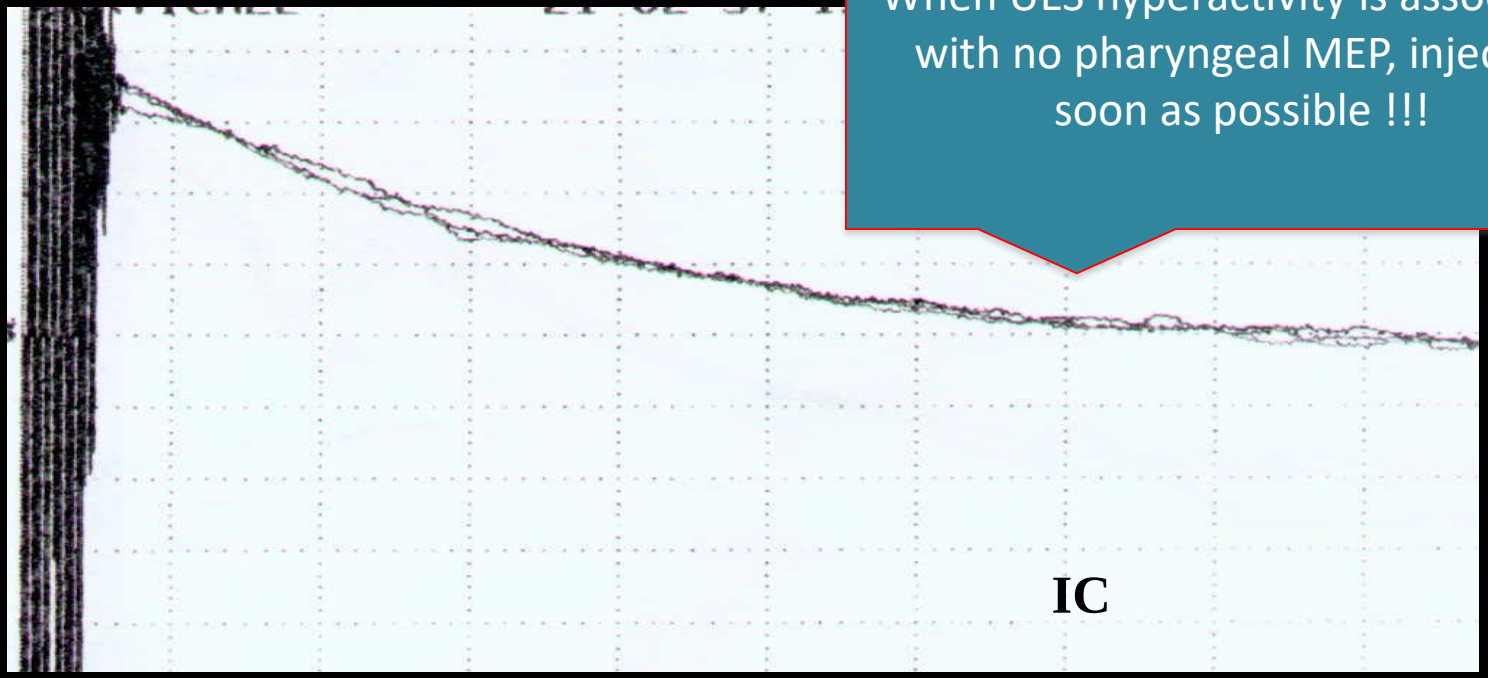
Quando trattare ?

- Se la disfagia con ipertono del UES presenta carattere di stabilità o di non miglioramento è corretto trattare anche se l'esordio dei disturbi della deglutizione è inferiore a 6 mesi

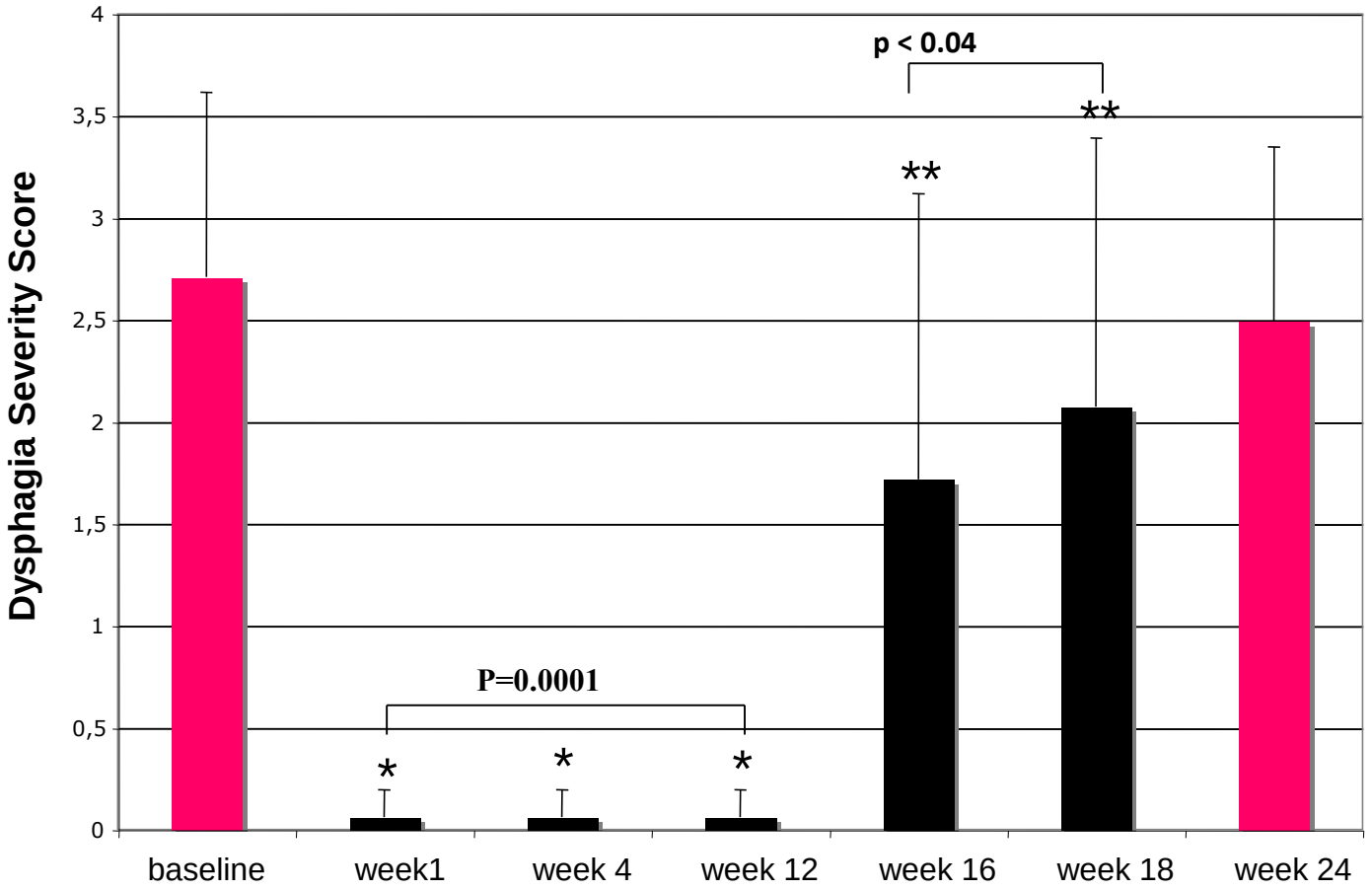
- In pazienti con disfagia da ictus ischemico/emorragico il paziente può essere trattato in fase subacuta (dopo un mese) qualora il miglioramento della disfagia sia assente o scarso

7 days after emispheric stroke

When UES hyperactivity is associated with no pharyngeal MEP, inject as soon as possible !!!



Dysphagia + no MEP = recovery is very unlikely !!!



Comparsa effetto: 4.1±1.1 giorni; durata media effetto: 14.6±2.1
Settimane (12-18 settimane); scomparsa disfagia in 83% dei pz;

Restivo unpublished data

frontiers in Pharmacology

ORIGINAL RESEARCH
published: 22 February 2017
doi: 10.3389/fphar.2017.00080

Botulinum Toxin Is Effective in the Management of Neurogenic Dysphagia. Clinical-Electrophysiological Findings and Tips on Safety in Different Neurological Disorders

Enrico Alfonsi[1], Domenico A. Restivo[2], Giuseppe Cosentino[3], Roberto De Icco[1,4], Giulia Bertino[5], Antonio Schindler[6], Massimiliano Todisco[1,4], Mauro Fresia[1], Andrea Cortese[1], Paolo Prunetti[1,4], Matteo C. Ramusino[1,4], Arrigo Moglia[1,4], Giorgio Sandrini[1,4] and Cristina Tassorelli[1,4]*

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TABLE 2 | Efficacy of BTX treatment in neurogenic dysphagia (1 month after BTX injection).

	Total	Parkinsonian syndromes			Stroke		Post-traumatic encephalopathy	Multiple Sclerosis
		PD	MSA-P	PSP	Cerebral lesion	Brainstem lesion		
Number of cases	67(%)	12	5	4	10	14	10	12
First injection of BTX								
High responder	35 (52%)	6 (50.0%)	2 (40.0%)	1 (25.0%)	7 (70.0%)	4 (28.6%)	8 (80.0%)	7 (58.3%)
Low responder	19 (28%)	4 (33.3%)	2 (40.0%)	1 (25.0%)	1 (10.0%)	7 (50.0%)	2 (20.0%)	2 (16.7%)
Non-responder	13 (19%)	2 (16.7%)	1 (20.0%)	2 (50.0%)	2 (20.0%)	3 (21.4%)	0 (0.0%)	3 (25.0%)
Second injection of BTX								
High responder	31 (46.3%)	2 (16.7%)	0 (0.0%)	0 (0.0%)	4 (40.0%)	3 (21.4%)	10 (100%)	3 (25.0%)
Low responder	22 (32.8%)	7 (58.3%)	4 (80.0%)	2 (50.0%)	5 (50.0%)	8 (57.2%)	0 (0.0%)	5 (41.7%)
Non-responder	14 (20.9%)	3 (25.0%)	1 (20.0%)	2 (50.0%)	1 (10.0%)	3 (21.4%)	0 (0.0%)	4 (33.3%)

First vs. second injection: $\chi^2 = 16.16$, $df = 4$, $p = 0.003$. PD, idiopathic Parkinson's disease; MSA-P, multiple system atrophy, parkinsonian variant; PSP, progressive supranuclear palsy.

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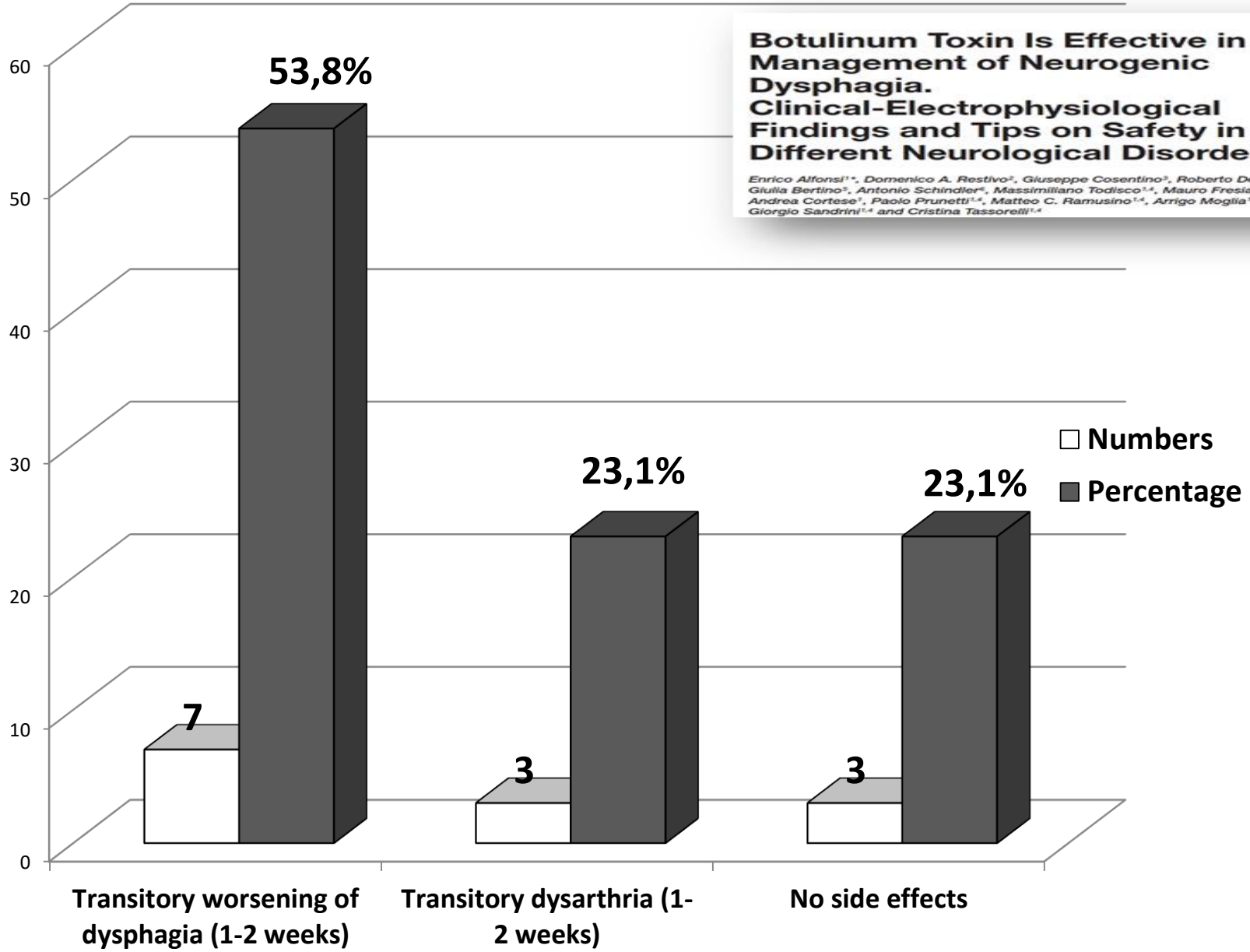
Non responders



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Other possible causes of ineffectiveness of treatment with botulinum toxin

- Diffusion of the toxin to nearby muscles such as, for example, the inferior constrictor of the pharynx (side effects: deficit of pharyngeal peristalsis , deficits of activity of infrahyoid muscles involved in UES opening, etc....)
- Injected dose lower than that required for the therapeutic effect
- Occurrence of immunogenic response (activity of antibody anti BTX)

Vantaggi Miotomia chimica

- **No effetti collaterali**
- **Trattamento non definitivo**
- **Ripetibile**
- **Eseguibile in pazienti defedati**
- **E' un marker di efficacia di una eventuale successiva miotomia chirurgica** *(Zaninotto et al., 2006)*

Conclusioni

- Il trattamento con tbx può essere efficace nel controllare disfagie associate ad ipertono del UES
- La tbx ha inoltre dimostrato la sua utilità come marker per la valutazione dell'efficacia della miotomia chirurgica
- La maggiore limitazione è legata al fatto che l'effettuazione del trattamento necissita di un'operatore esperto

THANK YOU