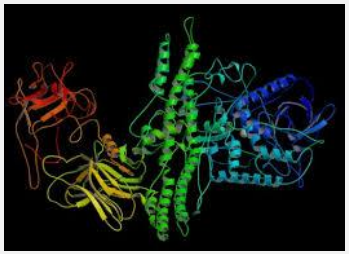
AZIENDA OSPEDALIERA SANTA MARIA TERNI



Trattamento con tossina botulinica nella malattia di Parkinson

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BoNT: FDA /EMA approved indications

• OnaA	• AboA	• IncoA	• RimaB
• Cervical dystonia • Axillary hyperhidrosis • Strabismus • Blepharospasm • Glabellar lines. • Prophylaxis of chronic migraines in adults • Upper limb spasticity in adult patients • Detrusor overactivity	• Cervical dystonia • Glabellar lines	• Cervical dystonia • Blepharospasm • Glabellar lines	• Cervical dystonia
• Hemifacial spasm • Focal spasticity associated with dynamic equinus foot deformity due to spasticity in ambulant paediatric cerebral palsy patients • Focal spasticity of the wrist and hand in adult post stroke • Hyperhidrosis of the axillae • Detrusor overactivity	• Blepharospasm • Hemifacial spasm • Spasticity in cerebral palsy • Lower limb post-stroke spasticity • Upper limb post-stroke spasticity	• Blepharospasm • Cervical dystonia • Upper limb post-stroke spasticity	

MP e BoNT: background

- Singolo centro in Canada, 1995-2014
- Solo 160 pazienti con sindrome parkinsoniana trattati con BoNT
- MP=117 / APD=36
- Studi di classi I solo per scialorrea e freezing della marcia

Cardoso, 2017

Sintomi motori e non motori nella malattia di Parkinson trattabili con BoNT

- Tremore
- Iperattività muscolare e/ attività spasmodica
  - Camptocormia, Sindrome di Pisa, Distonia cervicale, Discinesie da farmaci
- Disturbi della coordinazione fra gruppi muscolari:
  - Disfagia
  - Disfonia
- Condizioni associate a dolore
  - Contratture *off*, emicrania, ragade anale
- Disturbi vegetativi:
  - Scialorrea
  - Vescica iperattiva
  - Iperidrosi, Seborrea

MP: sintomi motori migliorabili con BoNT
1. tremore

- Pochi studi in aperto sul trattamento con BoNT del tremore refrattario ai farmaci
- Dosi abituali: 15 u negli estensori dell'avanbraccio e 50-100 u nei flessori di OnaA
- Il tremore migliora, ma spesso con associata debolezza della mano
- Un solo studio sul tremore mandibolare, con buona risposta alla dose di 30-100 u di OnaA

Cardoso, 2017

MP: sintomi motori migliorabili con BoNT
2. contratture muscolari localizzate

- Blefarospasmo (off, on)
- Aprassia di apertura delle palpebre (PSP)
- Bruxismo
- Distonia cervicale
  - Torcicollo, laterocollo, anterocollo
- Dolore lombare acuto o cronico
- Distonia del piede:
  - crampo doloroso del piede, distonia dell'alluce al risveglio (ELA)

Discinesie da farmaci dopaminergici

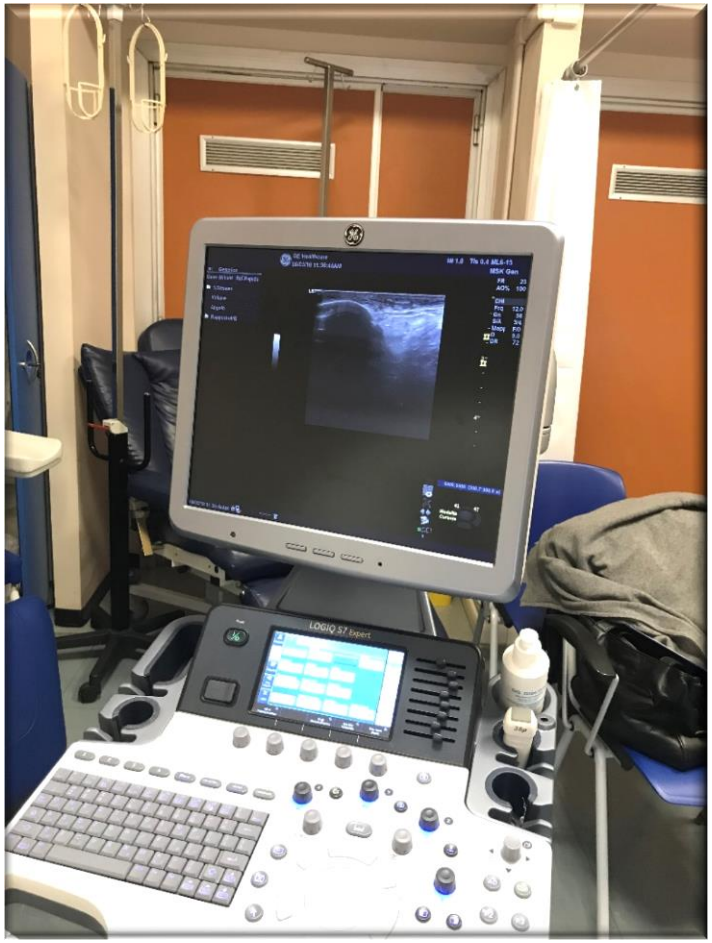
- Discinesie coreiche e coreo-distoniche in on / fasi di transizione
- Distonie craniocervicali
  - blefarospasmo, distonia cervicale
- Distonie dolorose in off
  - A volte le contratture in off

  possono essere molto dolorose,

  in particolare quelle dell'arto inf.

Distonie dolorose: quando trattare con la tossina botulinica?

- Quando il dolore è causato dalla contrattura distonica → gli stati dolorosi in off non correlati alla contrattura muscolare non rispondono alla BoNT
- La selezione dei muscoli deve essere orientata dalla presentazione clinica
- Muscolo Tibiale Posteriore: 50-150 u OnaA
- Necessario *targeting* guidato ECO o EMG


LOGIQ S7 Expert

Blefarospasmo

- Le dosi e i punti da iniettare vanno stabiliti con gli stessi criteri del blefarospasmo essenziale
- Nella aprassia di apertura i punti sono leggermente diversi perché il bersaglio è l'elevatore della palpebra
- I risultati del trattamento del blefarospasmo secondario (MP, sindromi tardive) sono sostanzialmente sovrapponibili a quelli ottenuti nelle forme primarie

Distonia cervicale

- Anterocollo (MP, MSA)
- Laterocollo (MP)
- Retrocollo (PSP)

BoNT utile per migliorare la postura e ridurre il dolore

Criteri di dose e scelta dei muscoli analoghi alle forme primarie

Disturbi assiali

HIGH LIGHT CME VIDEO

Camptocormia

Pathogenesis, classification, and response to therapy

Shaheda N. Azher, MD; and Joseph Jankovic, MD

Eziologia variabile?

Camptocormia: epidemiologia

	Country	Number of patients with PD	Prevalence (%)	Diagnostic criteria
Camptocormia				
Abe et al[8]	Japan	153	18%	45° TL flexion
Tiple et al[6]	Italy	275	7%	45° TL flexion
Lepoutre et al[9]	France	700	3%	TL flexion
Ashour and Jankovic[1]	USA	164	12%	45° TL flexion

Table: Prevalence studies of postural deformity in patients with parkinsonism

Doherty et al, Lancet Neurology 2011

Camptocormia: terapia con BoNT

Ultrasound-Guided Injection of the Iliopsoas Muscle with Botulinum Toxin in Camptocormia

Rainer von Coelln, MD,[1] Armin Raible, MD,[2] Thomas Gasser, MD,[1] and Friedrich Asmus, MD[1]*

[1]*Department for Neurodegenerative Diseases, Hertie Institute for Clinical Brain Research, University of Tuebingen, Tuebingen, Germany;* [2]*Department of Internal Medicine I, University of Tuebingen, Tuebingen, Germany*

TABLE 1. *Botulinum toxin A injections in parkinsonian patients with camptocormia, patient history, clinical features, and details of BTX treatment*

Patient	1	2	3	4
Sex	male	female	male	male
Age	75	75	73	70
Concomitant medical conditions	hyperthyroidism hypertension	depression	hyperlipidemia	CAD OSAS
Cause of parkinsonism	PD	MSA-P	PD	PD
Stage (Hoehn & Yahr)	III	IV	III	III
Duration of parkinsonism (yr)	16	3	8	10
UPDRS part III (on medication)	34	34	37	11
Duration of camptocormia (yr)	3.0	1.75	1.0	1.5
Direction of trunk bending	ventral	ventral	ventro-lateral (right side)	ventro-lateral (right side)
Response to levodopa: parkinsonism/ camptocormia	+/−	−/−	+/−	+/−
Side of BTX injection	bilateral	bilateral	right side	right side
Improvement (duration) and corresponding BTX dose	+(2 wk) 2× 500 MU	–	(+)(6 wk) 500 MU	–
Highest dose of BTX used	2× 1,500 MU	2× 1,000 MU	1,500 MU	1,500 MU
Side effects at highest dose (see text for details)	*	**	*	*

*Mild side effects

**Marked side effects, simultaneous worsening of MSA; wk, weeks; yr, years.

CAD, coronary artery disease; OSAS, obstructive sleep apnoea syndrome; PD, Parkinson's disease; MSA-P, multiple system atrophy, parkinsonian variant; UPDRS, Unified Parkinson's Disease Rating Scale; BTX, botulinum toxin type A (Dysport, Ipsen Pharma); MU, mouse units of BTX.

Injection of the Iliopsoas Muscle with Botulinum Toxin in Camptocormia

We have read with interest the paper by von Coelln et al., which was written about the failure on botulinum toxin type A (BoNT-A) ileopsoas injections for treating camptocormia associated with Parkinson's disease (PD) or multiple system atrophy.[1] We hade a similar experience treating two patients with advanced PD and severe camptocormia (defined generically as a reducible, forward flexion of the thoracolumbar spine of more than 45°), a symptom which usually responds poorly to dopaminergic treatment.[2]

Under CT guidance and using a posterior approach, 300 mU of BoNT-A (Botox, dilution: 100 mU/mL) was injected into the deep lumbar portion of each ileopsoas. Two points were injected on each side. Furthermore, the rectus abdominis was also injected bilaterally with 200 mU of BoNT-A. The total amount of BoNT-A injected on each session was 800 mU. The procedure was well tolerated; however, no objective or subjective improvement of camptocormia was observed 1 day, 1 week, and 2 weeks after the procedure.

We therefore confirmed that, even using an imaging-guided injection, which is time consuming but assures the correct placement in the muscle belly, this treatment is not effective for camptocormia associated with PD at least with the doses (which were comparable) used in the two studies. The object of future studies should be whether injection of higher doses of BoNT-A in the ileopsoas or targeting different spinal muscles is needed to achieve some positive clinical results in this disabling condition.

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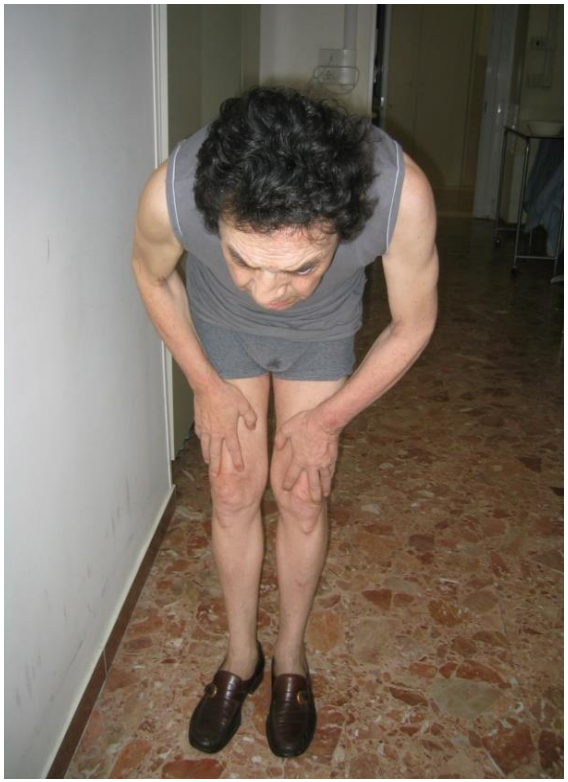

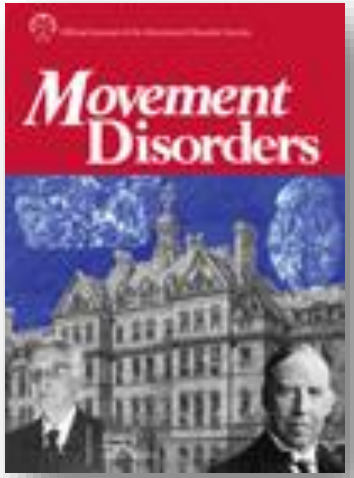

Movement Disorders
Vol. 24, No. 2, 2009, pp. 314–317

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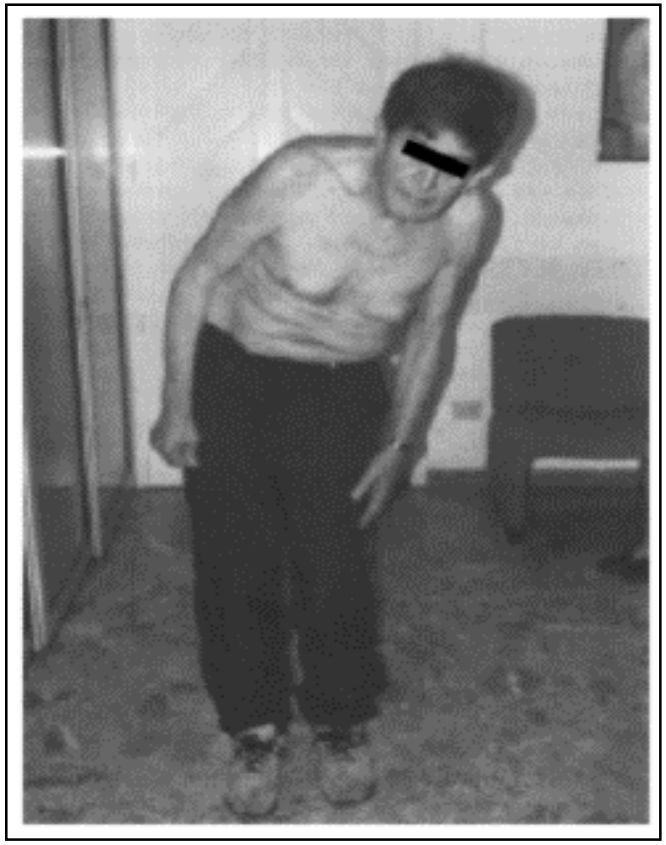
Synopsis of reports on the use of BoNT-A in camptocormia

Reference	Number of patients	Type of study	Duration of the follow-up	Targeting	Mean dose for session (U)	Results	Adverse events
Azher et al (2005)	9 patients with parkinsonism	Open	6 months	Injection of **rectus abdominus muscles**	300 to 600 U BoNT-A (Ona)	Marked improvement in 4 patients, lasting for about 3 months	Not reported
von Coelln et al (2008)	4 (3 PD, 1 MSA-P)	Open	4-6 months	Ultrasound-guided injection of **ileopsoas muscle**	500 to 1,500 U BoNT-A (Abo)	Subtle improvement in 2 PD, ineffective in 1 PD, worsening in MSA-P	Mild weakness hip flexors in 3 PD, simultaneous worsening of MSA
Colosimo et al (2009)	2 PD	Case series	2 weeks	Under CT guidance injection into the deep lumbar portion of each **ileopsoas** and in the **rectus abdominus**	800 mU BoNT-A (Ona)	Ineffective	Not reported
Fietzek et al (2009)	10 patients	Open	3 weeks	Ultrasound-guided injection of **ileopsoas muscle**	100 to 300 U BoNT-A (Inco)	Ineffective	Nor reported
Gerton et al (2010)	1 PD	Case report	_	Injection to the **rectus abdominus muscles**	180 to 360 U BoNT-A (Ona)	Ineffective	Not reported

Bertram & Colosimo, 2016

Sindrome di Pisa

Definizione (Ekbom et al, 1972)



Colosimo, MDJ 1998

Sindrome di Pisa e MP

Prevalenza

Pisa syndrome				
Bonanni et al[13]	Italy	1400	2%	>15° lateral flexion
Scoliosis				
Baik et al[14]	Korea	97	33%	Radiograph (Cobb method)
Ashour and Jankovic[1]	USA	164	9%	Lateral curvature
Grimes et al[15]	UK	103	60%	Clinical, radiography in 50%
Duvoisin and Marsden[16]	UK	21	91%	Clinical examination
Indo and Ando[17]	Japan	70	31%	Clinical examination
Serratrice and Schiano[18]	France	140	13%	Clinical then radiography
Sicard[19]	France	17	47%	NA
Onuaguluchi[20]	UK	33	15%	NA

Doherty et al, Lancet Neurology 2011

Movement Disorders
Vol. 22, No. 14, 2007, pp. 2097–2103

Video

Botulinum Toxin Treatment of Lateral Axial Dystonia in Parkinsonism

Laura Bonanni, MD, PhD,[1,2] Astrid Thomas, MD, PhD,[1,2] Sara Varanese, MD,[1,2]
Vincenzo Scorrano, MD,[1,2] and Marco Onofrj, MD[1,2]*

EMG guided
4 sites into the paraspinous muscles
level L2-L5 on the side of the trunk flexion, for a total dose of 500 Abo U.

blinded cross-over
with BoNT and placebo

9 patients

BoNT treatment was effective in 6 patients, there was only subjective benefit in 1 case, and no effect in the remaining 2

Synopsis of reports on the use of BoNT-A in Pisa syndrome

Reference	Number of patients	Type of study	Duration of follow-up	Targeting	Dosage (U)	Results	Side effects
Comella et al (1998)	5 patients with severe idiopathic (n=2) or tardive (n=3) truncal and cervical dystonia.	Case series	4 weeks	EMG guidance into the paravertebral muscles	150-300 BoNT-A (Ona)	Marked improvement in 3 patients	No adverse effects
Quirk et al (1996)	18 patients with nonoccupational limb and trunk dystonia	Open	4 weeks	EMG guidance	500 BoNT-A (Abo)	Improvement in 17 patients, marked in 3 patients	Excessive weakness in 5 patients
Santamato et al (2010)	1 PD	Case report	3 months	EMG recordings of paraspinal muscles	600 BoNT-A (Abo)	Slight improvement of axial inclination	No adverse effects
Bonanni et al (2007)	9 PD	Double blind randomized cross-over pilot study	3 months (In 4 patients treatment repeated for 2 years)	EMG recordings of paraspinal muscles	500 BoNT-A (Abo)	Effective in 6 patients. Subjective benefit in 1 patient. 2 patient did not reported any benefit	No adverse effects
Tassorelli et al (2014)	26 PD	Double blind randomized placebo-controlled study	6 months	EMG recordings of ileopsoas, paraspinal and rectus abdominis muscles	50-175 BoNT-A (Inco) Individually tailored	Effective for most outcome measures	Not reported

Bertram & Colosimo, 2016

Conclusioni: BoNT e distonia assiale nella MP

- Basso livello di evidenza
- Uso solo sperimentale
- Questioni aperte:
  - Quantificazione dell'effetto clinico
  - Effetto placebo
  - Dosi
  - Criteri di selezione dei muscoli e targeting
- Quale trattamento riabilitativo associare?

MP: disturbi migliorabili con la BoNT
3. disturbi vegetativi

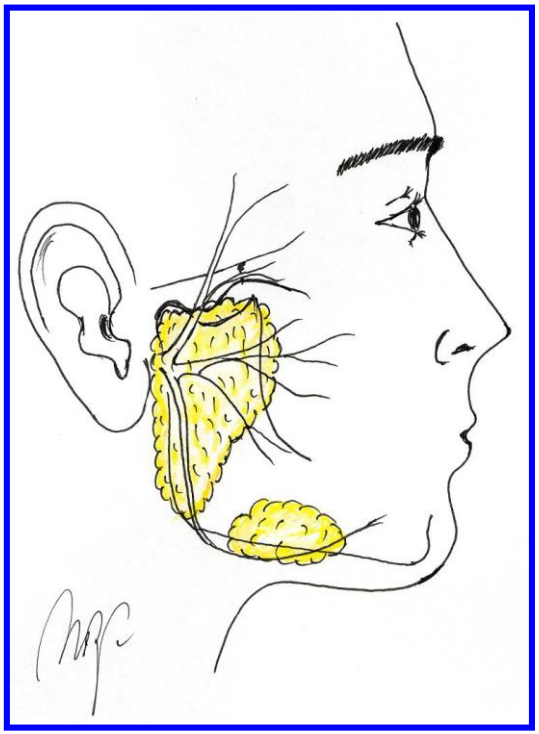
- Scialorrea
- Iperattività del detrusore vescicale
- Stipsi da dissinergia del pavimento pelvico
- Iperidrosi
- Seborrea?

Scialorrea

- Definizione: perdita di saliva involontaria dalla bocca
  non "ipersalivazione" !

- Meccanismi della deglutizione inefficaci
  - ± Sigillo labiale imperfetto
  - Capo inclinato in avanti

- Prevalenza nella malattia di Parkinson:
  - Fino al 40-80%
  - > in stadio avanzato



Vescica iperattiva

- Comune nella MP (35%) e ancora più nella MSA

- Causa di imbarazzo sociale e disabilità

- Studi controllati per altre condizioni, ma solo studi open nella malattia di Parkinson

- MDS EBM: *potentially useful*
  - Dosi: 100-200 Ona e 500 Abo
  - Efficace per 5-9 mesi
  - Effetti collaterali: ritenzione, ematuria, infezioni

Criteri Diagnostici per la Stipsi

Per almeno 12 settimane, non necessariamente consecutive, negli ultimi 12 mesi, due o più delle caratteristiche seguenti:

Sforzo in> ¼ defecazioni

Feci dure o coproliti in > ¼ evacuazioni

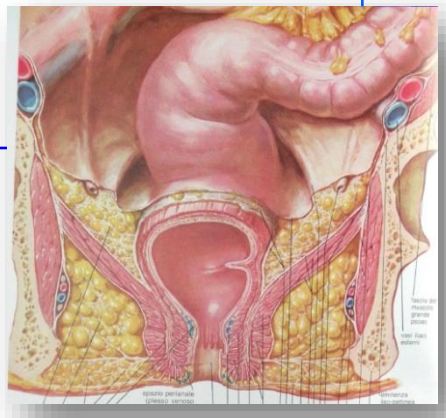
Sensazione di evacuazione incompleta > ¼ evacuazioni

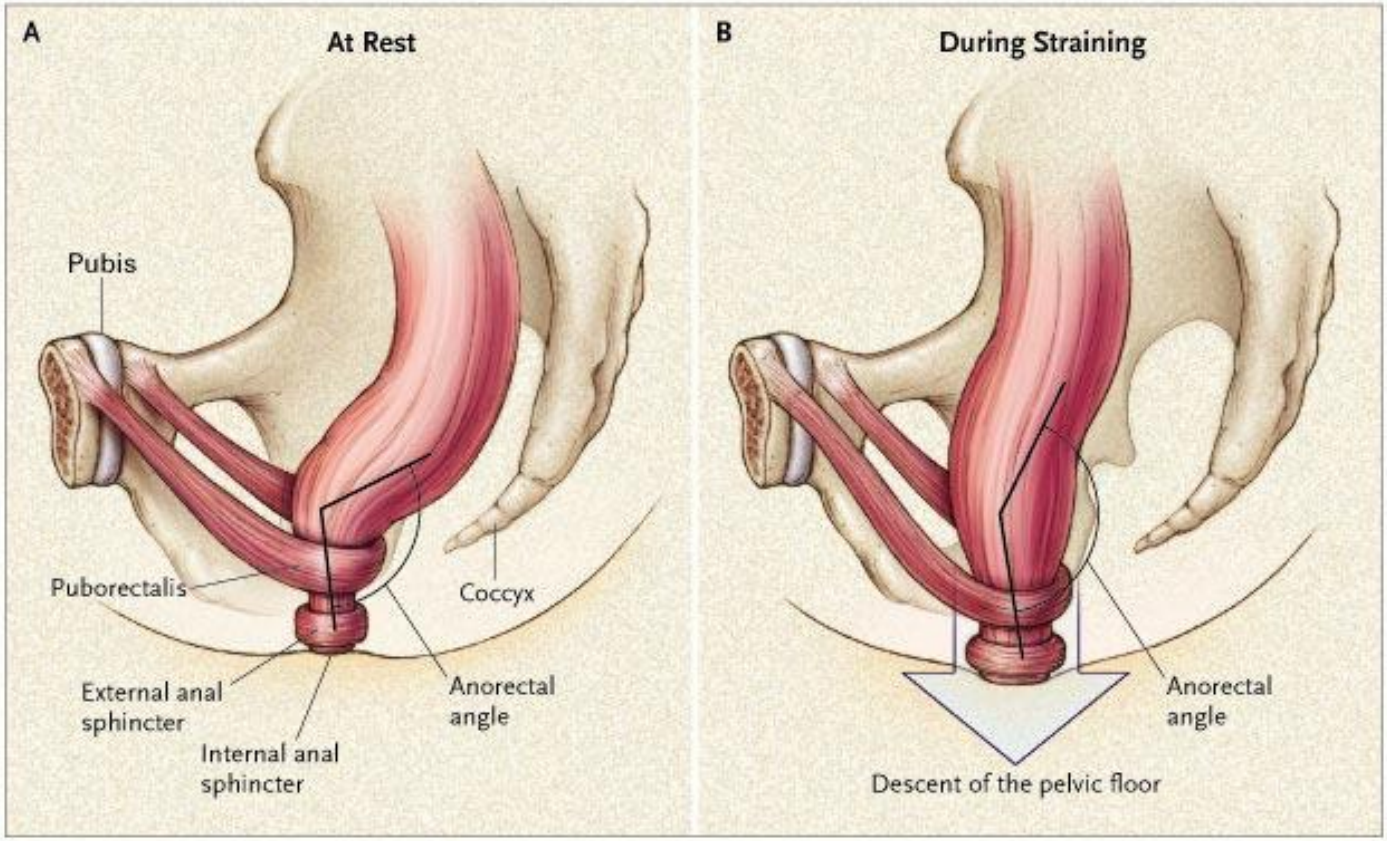
Sensazione di ostruzione anorettale / blocco in> ¼ evacuazioni

Manovre manuali per facilitare> ¼ evacuazioni

e / o <3 evacuazioni / settimana

Non ci sono criteri sufficienti per la sindrome del colon irritabile




A
At Rest
Pubis
Puborectalis
Coccyx
External anal sphincter
Internal anal sphincter
Anorectal angle
B
During Straining
Anorectal angle
Descent of the pelvic floor

Outlet type constipation in Parkinson's disease: results of botulinum toxin treatment

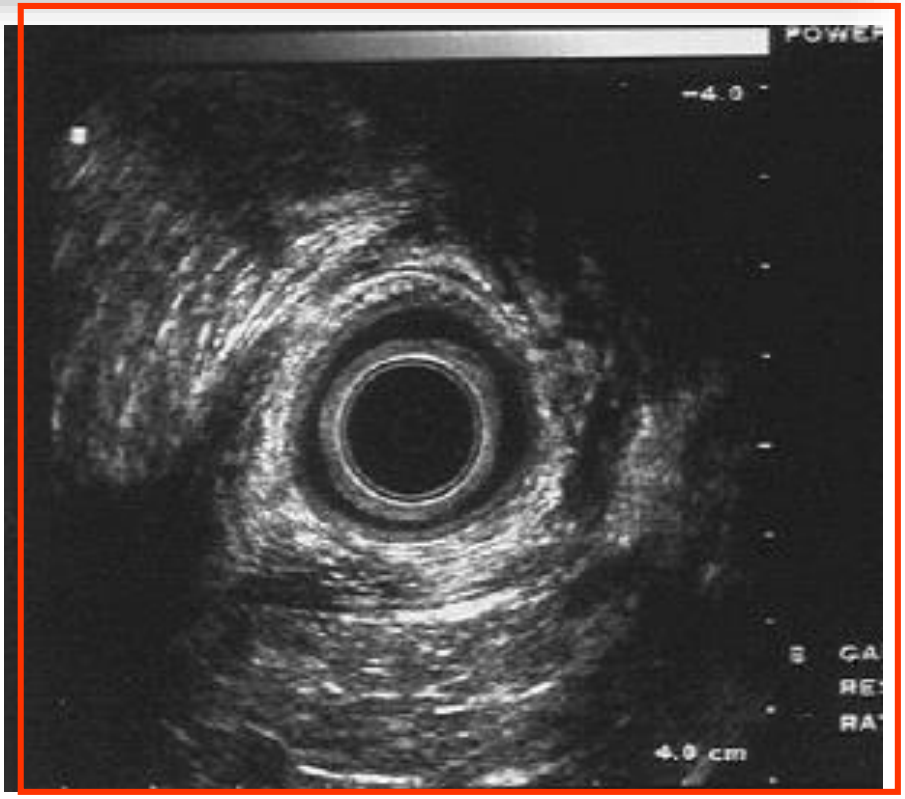
F. CADEDDU*, A. R. BENTIVOGLIO†, F. BRANDARA*, G. MARNIGA*, G. BRISINDA* & G. MARIA*
*Departments of *Surgery and †Neurology, Catholic School of Medicine, University Hospital Agostino Gemelli, Rome, Italy*

Accepted for publication 22 August 2005

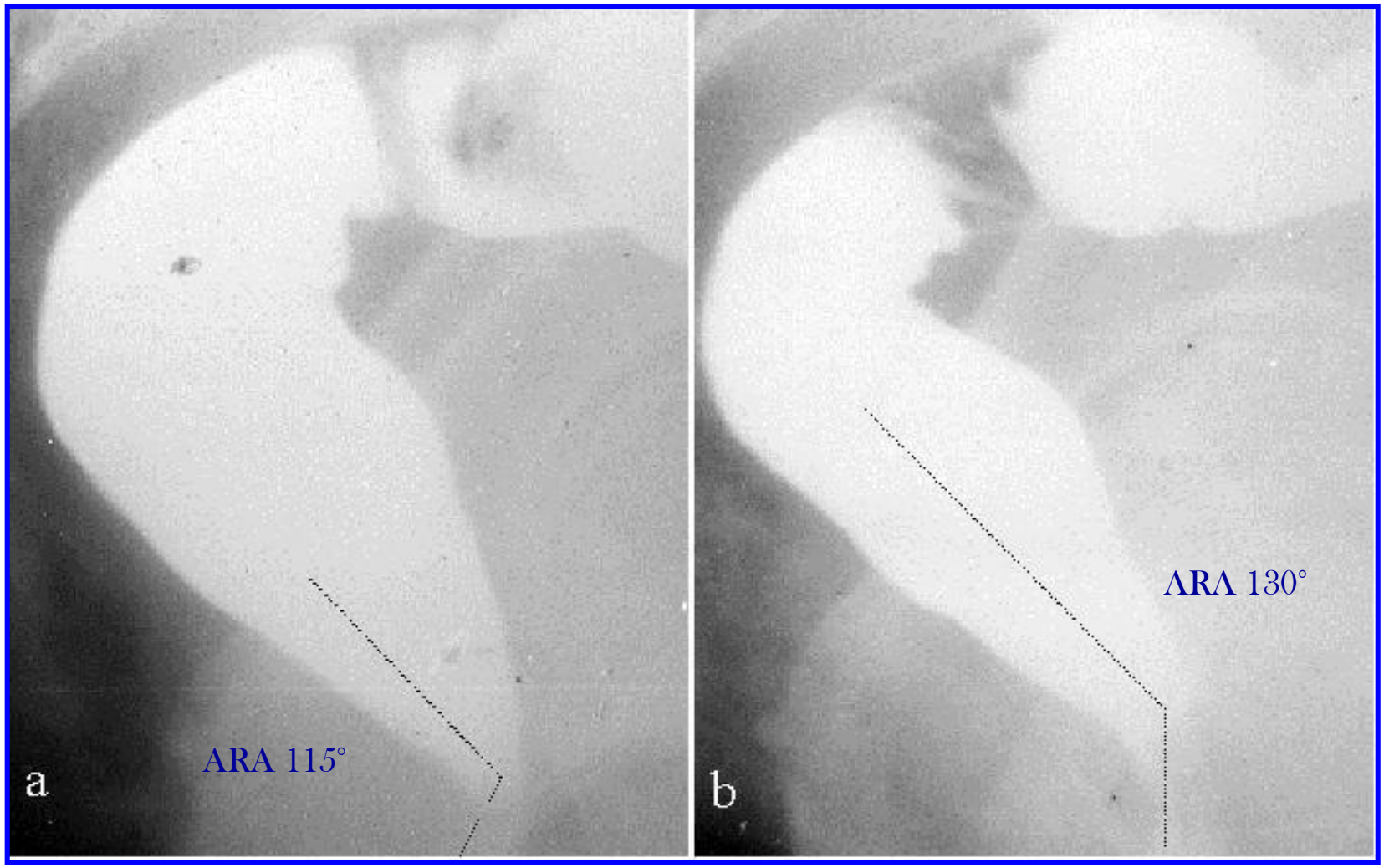
Background: Constipation is one of the most common autonomic dysfunctions observed in Parkinson's disease.

Aim: To investigate the efficacy of injections of botulinum toxin in improving rectal emptying in these patients.

Methods: Eighteen Parkinson's disease patients with outlet constipation were included in the study. The patients were treated with type A botulinum toxin, injected into two sites on either side of the puborectalis muscle under ultrasonographic guidance.



Defecatory proctography on straining before (a) and after the treatment (b)



Conclusioni

- Molteplici indicazioni
- Trattamento altamente individualizzato
- **Poche evidenze, ma sempre da considerare:**
  - In caso di distonia focale off o non off-relata quando è colpito il distretto cervicale
  - Quando la distonia è dolorosa
  - Quando la distonia è un sintomo focale invalidante (es. distonia dell'alluce: dolore, difficoltà di deambulazione, ostacolo a calzare le scarpe)
  - Per la scialorrea
  - Per la grave stipsi da dissinergia del pavimento pelvico (10%)