Surgical Treatment of Dystonia

our experience and literature evidences

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“... the disease has something quite unique; namely the severe tonic cramps particularly in the neck, head and the proximal sections of the extremities. The unique “torqued” gait is practically pathological. The prognosis is bad. All therapeutic attemps are as of yet unsuccessfull...”

_Hermann Oppenheim, 1911_
New Perspectives on Dystonia
Melanie Langlois, Francois Bicher, Sylvain Chouvard

ABSTRACT: Dystonia is a syndrome of sustained muscular contractions with numerous underlying etiologies. This review examines the varied phenomenology of dystonia, its evolving classification including recent genetic data as well as its clinical investigations and treatment. Although age of onset, anatomical distribution and family history are key elements of the investigation of dystonia, classification increasingly relies on etiological and genetic criteria. Physiological abnormalities in striatocortical circuits are common in dystonia but the pathophysiology is still unclear. In recent years, a great deal has been learned on the more common primary dystonias such as primary torsion dystonia and on dystonia-plus syndromes such as dopamine responsive dystonia. Treatment of dystonia has also evolved and there are now a number of therapeutic agents with close beneficial effects including anticholinergics, benzodiazepines, and botulinum toxin and there is growing interest in neurosurgical surgery including deep brain stimulation.

Table 1: Classification of dystonia by distribution

A. Focal involvement of one body part
1. Eyelids: blepharospasm
2. Mouth: oromandibular dystonia; embouchure dystonia
3. Larynx: dystonic adductor dysphonia or whispering dysphonia
4. Neck: cervical dystonia
5. Hand and arm: writer’s cramp, occupational dystonia, musician’s dystonia, yips

B. Segmental: involvement of two or more contiguous body parts
1. Cranial; two or more parts of cranial and neck musculature affected
2. Axial; neck and trunk affected
3. Brachial; one arm and axial; both arms, +/- neck, +/- trunk
4. Cervical: one leg and trunk; both legs, +/- trunk

C. Multifocal
1. Two or more non-contiguous parts affected

D. Generalized
1. Combination of segmental cranial dystonia in combination with any other segment

E. Hemidystonia
1. Ipsilateral arm and leg affected

Table 2: Classification by etiology

A. Primary
1. Early-onset primary torsion dystonia - PTD - DYT1 - TORY1A
2. Early-onset segmental/cranial - DYT1
3. Whispering dystonia - DYT2
4. Adult-onset familial dystonia - DYT7
5. Mixed - planumtype dystonia - DYT8
6. Spastic, adult-onset focal dystonia
   a. Blepharospasm
   b. Oromandibular dystonia
   c. Spasmodic dysphonia
   d. Cervical dystonia
   e. Occupational dystonia
   f. Trunk dystonia
   g. Others

B. Dystonia-plus syndromes
1. Primary dystonia plus syndrome
   a. Dopa-responsive dystonia
      i. DYT6 (dopamine hydroxylase 1 deficiency)
      ii. Tyrosine hydroxylase deficiency
      iii. Gpi-1 involved in dopamine synthesis deficiency
      iv. Pihlta-carbinolamine dehydratase deficiency
      v. Dihydrolipoyl reductase deficiency
   b. Dopa-responsive dystonia plus syndrome
      i. Aromatic amino acid decarboxylase deficiency
      ii. Rapid-onset dystonia-parkinsonism - DYT12
   c. Dystonia with myoclonus
      i. Dystonia plus myoclonus

C. Spasmodic dystonia
1. Familial cervical dystonia
2. Benign essential blepharospasm
3. Cervical dystonia
4. Cervical dystonia with blepharospasm
5. Upper motor neuron syndrome
6. Parkinsonian blepharospasm
7. Trigeminal neuralgia
8. Facial dystonia
9. Multiple sclerosis
10. Drug-induced
11. Levodopa
12. Dopa receptor blocking dopamine agonists
13. Neuroleptics

D. Heredodegenerative diseases
1. Mitochondrial disorders
2. Huntington’s disease
3. Machado-Joseph disease
4. Dystrophia myotonica
dystrophica
5. Dystrophia myotonica
dystrophica
6. Dystrophia myotonica
dystrophica
7. Dystrophia myotonica
dystrophica
8. Dystrophia myotonica
dystrophica
9. Dystrophia myotonica
dystrophica
10. Dystrophia myotonica
dystrophica

E. Pseudodystonias
1. Myotonic dystrophy
2. Ocular myotonia
3. Malignant hyperthermia
4. Dystrophia myotonica
5. Dystrophia myotonica
6. Dystrophia myotonica
7. Dystrophia myotonica
8. Dystrophia myotonica
9. Dystrophia myotonica
10. Dystrophia myotonica

DYSTONIA CLASSIFICATION

Age of onset
- Childhood (early onset dystonia)
- Adolescence
- Adulthood (30-50 years)
> 50 years (Late onset dystonia)

Bodily distribution of symptoms
- Focal dystonia
- Segmental dystonia
- Multifocal/Multisegmental
- Generalized

Cause
primary or idiopathic ()
- genic faulty (ereditary or sporadic generally early onset )
- no genic faulty (often late onset)

secondary

heredo-degenerative
- 15 Patients: 9 primary Dystonia - 4 DYT-1 positive

- Best effect on **primary** dystonia: significant improvement in secondary but lower than primary Dystonia

- DBS no difference with lesional technique but **reversible**
Electrical stimulation of the globus pallidus internus in patients with primary generalized dystonia: Long-term results.

- Generalized Dystonia
- 30% of cases DYT-1 positive
- similar results in DYT-1 positive and negative patients

Krauss Jk, Lober TJ, Weigel R, Canelle HH, Weber S, Burgunder JM:
Chronic stimulation of the globus pallidus internus for treatment of non-dYT1 generalized dystonia and choreoathetosis: 2-year follow up.

- Similar results in DYT-1 negative patients (6) respect to DYT-1 positive
-17 patients: 10 primary
  4 DYT positive

- DYT-1 negative more inhomogeneous results
- Prospective, controlled, multicenter study, NEJM, 2005
- 22 patients (7 DYT-1 positive)
- **BFMDR scale improvement** from $46.3 \pm 21.3$ to $21.0 \pm 14.1$ at 12 months follow-up
- *not statistical evidence of best improvement in DYT-1 positive cases*
- Randomized, controlled clinical trial: between stimulation and shamimulation in 40 implanted patients (NEJM, 2006)
- Improvement in BFMDR scale, disability and quality of live (SF-36),
- any statistical difference between DYT-1 positive and negative improvement
- Similar effect between generalized and segmental dystonia
- 10 patients with **cervical dystonia** followed for 31.9 ± 20.9 months
- Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) severity score **improved by 54.8%**
- TWSTRS disability score **improved by 59.1%**
- TWSTRS pain score **improved by 50.4%**
Bilateral, pallidal, deep-brain stimulation in primary
generalised dystonia: a prospective 3 year follow-up study.


INSERM U679, Neurology and Experimental Therapeutics, Groupe Hospitalier Pitié-Salpêtrière, Paris, France. marie.vidailhet@sat.aphp.fr

BACKGROUND: We have previously reported the efficacy and safety of bilateral pallidal stimulation for primary generalised dystonia in a prospective, controlled, multicentre study with 1 year of follow-up. Although long-term results have been reported by other groups, no controlled assessment of motor and non-motor results is available. In this prospective multicentre 3 year follow-up study, involving the same patients as those enrolled in the 1 year follow-up study, we assessed the effect of bilateral pallidal stimulation on motor impairment, disability, quality of life, cognitive performance, and mood. METHODS: We studied 22 patients with primary generalised dystonia after 3 years of bilateral pallidal stimulation. We compared outcome at 3 years with their status preoperatively and after 1 year of treatment. Standardised video recordings were scored by an independent expert. Data were analysed on an intention-to-treat basis. FINDINGS: Motor improvement observed at 1 year (51%) was maintained at 3 years (58%). The improvement in quality of life (SF-36 questionnaire) was similar to that observed at 1 year. Relative to baseline and to the 1 year assessment, cognition and mood were unchanged 3 years after surgery, but slight improvements were noted in concept formation, reasoning, and executive functions. Pallidal stimulation was stopped bilaterally in three patients because of lack of improvement, technical dysfunction, and infection, and unilaterally in two patients because of electrode breakage and stimulation-induced contracture. No permanent adverse effects were observed. INTERPRETATION: Bilateral pallidal stimulation provides sustained motor benefit after 3 years. Mild long-term improvements in quality of life and attention were also observed.

LANCET NEUROLOGY, 6: 223-229, 2007
How does DBS work?

stimulation-induced alterations in the activation of voltage-gated currents that block neural output near the stimulating electrode (depolarization blockade)

indirect inhibition of neuronal output by means of activation of axon terminals that make synaptic connections with neurons near the stimulating electrode (synaptic inhibition)

synaptic transmission failure of the efferent output of stimulated neurons as a result of transmitter depletion (synaptic depression)

stimulation-induced disruption of pathologic network activity

(Beurrier et al., 2001); (Dostrovsky et al., 2000); (Urbano et al., 2002); (Montgomery and Baker, 2000).
stimolazione cerebrale profonda: **DBS**

tecnica di “neuromodulazione” che sfrutta l’impianto di stimolatori cronici multipolari.
Inibizione funzionale mediante stimolazione ad alta frequenza di specifici bersagli encefalici.
“Uncovering the details of the mechanisms of DBS will depend on more complete definitions of the changes in neural activity generated in the stimulated, efferent, and afferent nuclei of the basal ganglia and cortex”

Deep brain stimulation in the treatment of severe dystonia.
Vercueil L, Pollak P, Fraix V, Caputo E, Moro E, Benazzouz A, Xie J, Koudsie A, Benabid AL.

- GPi more effective target on symptoms control

Deep brain stimulation for dystonia confirming a somatotopic organization in the globus pallidus internus.


CONCLUSIONS: Inside the posterolateroventral subvolume of the GPi on the right side, three statistically different locations of electrode contacts were determined to be primary deep brain stimulation treatment sites for particular body parts in cases of dystonia.
STIMOLAZIONE CEREBRALE PROFONDA
DEL GLOBUS PALLIDUS INTERNO NELLA DISTONIA

1. RAZIONALE
2. INDICAZIONI CLINICHE
3. SELEZIONE PAZIENTI E FOLLOW UP
4. CASISTICA FERRARA
primary dystonia results from a functional disturbance of the basal ganglia, particularly in the striatal control of the globus pallidus (and substantia nigra pars reticulata). This causes altered thalamic control of cortical motor planning and executive areas, and abnormal regulation of brainstem and spinal cord inhibitory interneuronal mechanisms.

Brain, Berardelli et al, 1998
Fisiopatologia della distonia

- Eccessiva coattivazione mm agonisti-antagonisti
- Overflow: coinvolgimento della mm sinergica
- Coinvolgimento sensitivo: "trucchi sensoriali"
Multilevel abnormalities

Spinal Cord

Brainstem

Cortex

Lorenzano et al, 2000

Berardelli et al, 1984

Currà et al, 2000
Modelli fisiopatologici della distonia

- Deficit dei meccanismi inibitori troncali e spinali (inibizione reciproca)

- Modificazione dell’eccitabilità intracorticale e corticospinale (studi TMS)

- Ipometabolismo striatale ed iperattivazione aree associative frontali, ridotta attivazione area 4

- Dissociazione lenticolo-talamica (studi PET)

  Alterazione delle connessioni tra gangli della base (Globus Pallidus Internus e/o Talamo) e aree corticali (AMS) con

  iperattività della via diretta
Focusing and Scaling Hypothesis
(Vitek 1988)
MODELLO DISTONIA PRIMARIA

NORMAL

CEREBRAL CORTEX

STRIATUM

D2
D1

GPe

SNC

STM

GPI/SNr

DYSTONIA

CEREBRAL CORTEX

STRIATUM

D2
D1

GPe

SNC

STM

GPI/SNr

VIA DIRETTA

VIA INDIRETTA
Stimolazione cerebrale profonda del Globus Pallidus internus: razionale

anni 90: risultati della Pallidotomia nei pazienti con Malattia di Parkinson con miglioramento evidente sulla discinesia/distonia levodopa indotta

primi esperimenti soddisfacenti in pazienti con distonia primaria DY1 + positiva

Stimolazione cerebrale profonda del Globus pallidus internus: effetto reversibile e meno gravato da rischi
INDICAZIONI CLINICHE
DBS GPi per DISTONIA

Indicazione:

• **Distonia generalizzata**
  - primaria
  - secondaria

• **Segmentale (cervico-assiale)**
  - primaria
  - secondaria

• **Distonia focale (cervicale)**

  - Palliativa
    - spasmi muscolari
    - Difficoltà deglutitorie
DYT 1+ Children

% improvement

follow-up (months)

Popolazione
51 bambini
(novembre 1996-novembre 2005)
17 DYT +
Miglioramento 90.3 %

Treatment of DYT1-generalised dystonia by stimulation of the internal globus pallidus

Philippe Coubes, Agathe Rouberte, Nathalie Vayssiere, Simone Hemm, Bernard Echenne

In seven selected patients with dystonia muscologica deformans-1 generalised dystonia (DYT1), continuous bilateral stimulation of the globus pallidus internus was associated with substantial improvement of dystonia and functional disability.

P. Coubes 2005
DYT 1- Children

9 bambini
Miglioramento : 80%

P. Coubes 2005
Postanoxic cerebral palsy

7 bambini
Miglioramento
del 30-40%

followup (months)

% improvement

P. Coubes 2005
Pkan

Neurodegenerazione associata a deficit di pantotenato-kinasi

4 bambini

followup (months)

% improvement

P. Coubes 2005
RISULTATI

• DISTONIA PRIMARIA:
  • DYT-1 + miglioramento 60-100% (Coubes ’00-05)
  • Molte altre pubblicazioni confermano tali percentuali in forme “primarie” focali o generalizzate (Fogel 2005, Tronner 2004; Lozano 2005)

• DISTONIA SECONDARIA
  • Risultati incerti (10-30%)
  • Miglioramento “non drammatico”
  • Scale di valutazione non adatte a valutare outcome
  • Miglioramenti possibili anche a distanza di molti mesi
  • non altre opzioni terapeutiche!

• FORME EREDODEGENERATIVE:
  • Solo casi selezionati
  • Scale esistenti non adatte a valutare outcome
  • Miglioramenti anche a distanza di diversi mesi
Risultati

- Tollerabilità nei bambini eccellente

- Efficacia evidente nel trattare il sintomi distonia/discinesia soprattutto se isolato e non inserito in altri quadri sindromici

- Efficacia comparabile solo in casi selezionati di tipo secondario o eredodegerativo

- non perdita di efficacia nel tempo (follow-up di 9 aa)
Centro per i disturbi del movimento di
Azienda Universitaria-Ospedaliera
S.Anna Ferrara

SELEZIONE PAZIENTI DISTONICI
Selection Criteria

• Pz in cui il “miglioramento atteso” > “rischi chirurgici”

• Distonia come “disabilità” (identificare altre sorgenti di disabilità)

• Forme generalizzate con grave “impairment motorio”

• Forme segmentali gravi e non altrimenti tratabili (“non responder” a BoNT)

• Aspettative pz e famiglia
quando operare?

- Sempre forme “primarie generalizzate” (DYT1 + o -)

- Forme evolutive

- Grave disabilità (anche forme “focali” insensibili alle comuni terapie)

- Forme secondarie → solo casi selezionati

- Valutazione preliminare altre terapie possibili (ITB ?)
quali forme?

- Miglioramento precoce e più evidente della distonia mobile con movimenti involontari di tipo tremore mioclonico, ballistico...
- Miglioramento importante della componente algica associata
- Miglioramento secondario della distonia “fissa”
- Risultati variabili sulla disfonia
- RMN cerebrale normale (criterio predittivo positivo di outcome migliore)
- Esclusione dei pazienti con retrazioni tendinee
come valutare?

- Scale cliniche “criticate”
- Importanza “video” (???)
- Unifed Dystonia Rating Scale $\rightarrow$ criticata (troppo complessa)
- Global Dystonia Scale $\rightarrow$ criticata (troppo semplice)
- Burke-Fahn-Marsden Scale $\rightarrow$ preferita
• valutazione scala clinica “Burke-Fahn-Marsden Dystonia Rating Scale” + video, “in doppio cieco”

- Pre-intervento
- Post-intervento (a 3, 6, 12, 24, 36, 48, mesi.....)

### Scala Motoria

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<th>REGIONE</th>
<th>FATTORE PROVOCANTE</th>
<th>GRAVITÀ</th>
<th>FATTORE PESO</th>
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<td>O - 4</td>
<td>O - 4</td>
<td>0.5</td>
<td>O - 8</td>
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<td>bocca</td>
<td>O - 4</td>
<td>O - 4</td>
<td>0.5</td>
<td>O - 8</td>
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<td>ling / deglut</td>
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<td>O - 4</td>
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<td>0 – 16</td>
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<td>O - 4</td>
<td>O - 4</td>
<td>1</td>
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<td>Al sx</td>
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**Totale** 0 - 120

### Scala Funzionale

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<td>vestirsi</td>
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<tr>
<td>deambulazione</td>
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**Totale** 0 - 30
Screening “pre-intervento”

- Test neuropsicologici (studio particolareggiato funzioni linguistiche, f. frontali) + valutazione psichiatrica

- PEV – visita oculistica con CV

- Scala clinica (video) → BFMS per le generalizzate o TWSTRS per le forme cervicali

- PEM / EEG
CASISTICA FERRARA
**POPOLAZIONE** 22 pazienti dal 2001 al 2008 (10 M, 12 F)

- 19 pz con follow-up minimo di 6 mesi
  - età media: 40 aa (range 25-64 aa)
  - distonia generalizzata o multisegmentaria
  - durata media di malattia: 22 aa (range 8-54 aa)

**SCREENING PRE-OPERATORIO**
- RM cerebrale, test NPS, PEV

**DBS n.GPI bilaterale**
- MR stereotassica
- anestesia locale
- monitoraggio clinico e neurofisiologico intraoperatorio
  - Microregistrazione, microstimolazione + macrostimolazione
- verifica del corretto posizionamento degli elettrodi con RMN post-operatoria
Casistica

- Pazienti suddivisi in tre categorie
  - 13 pz con distonia primaria
  - 4 pz con distonia secondaria (da lesioni cerebrali focali)
    - 1 da ipossia perinatale
    - 2 da kernicterus
    - 1 da ictus
  - 2 pz con forme eredodegenerative
    - 1 Sindr. di Leigh
    - 1 DYT3-X-linked-Dystonia-parkinsonism, Lubag
  - calcolo media punteggi e miglioramento clinico percentuale
Target Localization: GPi

Morphological MRI - direct target identification
in T2 sequences

MRI - indirect way (AC-PC)
Variable localization - related to III Ventricule’s dimension
from 18 to 22 mm from midline;
from 0 m to 6 mm anterior to midcommissural point;
from 1 mm to 7 mm inferior to AC-PC

MRI - indirect way (anatomical landmark)
Optic tract - III Ventricule’s floor
External Lamina esterna (between GPe-GPi)
Posterior Mamillary Bodies

Mixed Merging Techniques
Possible error because: “invisible” target
anatomical variability
RM distorsion (maximum error on Y coordinate)
Coronal plane 2 mm anterior to bicommissural midpoint

What is the best track?
Laitinen theoric target and optimal electrode’s track

Coronal plane

Axial plane
Stereotactic Target Localization through "Framelink®" software

MR track simulation
(T1 - T2 sequences merged)

MR track simulation with Schaltenbrandt Atlas overlapping
Great anatomical variability between patients and between two side of some patient

Great anatomical variability of functional subvolume of GPi

**TARGET LOCALIZATION**

**MER** - multiple track recording

Microrecording to **identify nucleus** - passive movement

Microstimulation define neighbouring **eloquent structures**

VEP confirming **Optic tract** localization (below GPi)

Different **Discharge Patterns**
Typical discharge pattern multi-track microrecording

GPe/GPi
**Primary Dystonia**

Mean thickness: 5.1 mm  
Pattern: regular/irregular/burst  
High frequency discharge 70-250 Hz  

Border cells  
from -11 to -9 mm  

Irregular discharge  
70 - 170 Hz  
from -9 to -5 mm  

High frequency discharge 120-250 Hz  
from -5 to 0 mm
Monopolar semi-microelectrode
Bipolar semi-microelectrode
macroelectrode
Post-operative MRI
C.C., 28 aa, F
Complessive BFMDR motor score on 16 patients

3 months < follow-up < 3 years
Distonie primarie - BFMRS motorio

% miglioramento vs basale
Distonie primarie - BFMRS funzionale

- linguaggio
- scrittura
- alimentazione
- nutrizione
- igiene
- vestirsi
- camminare
- totale

% miglioramento vs basale
BFMDR motor score at 3 years follow-up

2 patients PRIMARY DYSTONIA

BFMDR motor score at 2 years follow-up

2 patients PRIMARY DYSTONIA
BFMDR disability score at 3 years follow-up

2 patients

BFMDR disability score at 2 years follow-up

2 patients
BFMDR motor scale at 6 months / 1 year follow-up

3 patients HEREDO-DEGENERATIVE DYSTONIA

BFMDR disability scale at 6 months / 1 year follow-up

3 patients HEREDO-DEGENERATIVE DYSTONIA
DISTONIA SECONDAria

- Lesione nucleo lenticolare controlaterale (putamen)
- Studi PET: iperattivazione area 4
- Minor risposta al trattamento chirurgico (pallidotomia o DBS regione posteroventrale del Gpi)

Interessamento di altre aree corticali o sottocorticali nella genesi del disturbo
BFMDR motor score at 1 year follow-up

3 patients GENERALIZED SECONDARY DYSTONIA

BFMDR disability score at 1 year follow-up

3 patients GENERALIZED SECONDARY DYSTONIA
- Best effect on primary generalized dystonia (specially DYT-1 positive) 60-70%

- Lower clinical improvement on BFMDRS in secondary generalized 10-15%

- Medium effects in heredo-degenerative cases 35-40%

Last 3 patients are too early implanted (2008) to evaluate results
Concluding

DBS represents an effective treatment for generalized and segmental dystonia for patients with insufficient clinical outcome or intolerable side effect of medical treatment.

GPI is, actually, the best target.

Target focusing with intraoperative MER is critical for best clinical outcome.

Secondary dystonia is less controlled, but we reported clinical improvement.

Our data suggest clinical outcome improve until our maximum 3 years follow-up.

DBS treatment is safe and completely reversible.