DEEP BRAIN STIMULATION IN CHILDREN

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# Phenomenologic Classification of Pediatric Movement Disorders

<table>
<thead>
<tr>
<th>Movement Disorder</th>
<th>Brief Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tics</td>
<td>Stereotyped intermittent, sudden, discrete, repetitive, nonrhythmic movements, most frequently involving head and upper body.</td>
</tr>
<tr>
<td>Chorea/ballismus</td>
<td>Chaotic, random, repetitive, brief, purposeless movements. Rapid, but not as rapid as myoclonus. When of very large amplitude, choreic limb movements often are called ballismus.</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Repetitive, sustained, abnormal postures and movements. Abnormal postures typically have a twisting quality.</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Sudden, brief, shocklike movements that may be repetitive or rhythmic.</td>
</tr>
<tr>
<td>Stereotypy</td>
<td>Patterned, episodic, repetitive, purposeless, rhythmic movements.</td>
</tr>
<tr>
<td>Tremor</td>
<td>Rhythmic oscillation about a central point or position involving one or more body parts.</td>
</tr>
<tr>
<td>Parkinsonism</td>
<td>Hypokinetic syndrome characterized by rest tremor, slow movement (bradykinesia), rigidity, and postural instability.</td>
</tr>
</tbody>
</table>

Schlaggar, Mink 2003
DIAGNOSIS

PKAN
mitochondrial encephalopathy
hypoxic ischemic encephalopathy

Koy, 2016
Transient/Permanent

Age-dependent

Age at onset, phenomenology and extent orientate towards etiology

Complexe dystonia rather in acquired and progressive disorders
DYSTONIA

- Often unremitting (most frequent lasting movement disorder in children)
- Early spread of symptoms (generalized)
- Increasing disability
- Eventually life-threatening conditions
- No efficient pharmacological therapy
- Side effects of medication/cognitive impact insufficiently assessed
MEDICAL TREATMENT

- Little evidence from controlled trials on the best therapeutic strategies (Trihexyphenidyl, Fahn, 1983)
- Heterogeneity in the pharmacological management of pediatric dystonia
- Mostly related to personal experience, drugs availability, ...
- The higher number of treatment -proxy measure for non responsiveness and severity of the movement disorder
- L-dopa trial mainly for isolated dystonia and patients with symptom fluctuations not to miss a DRD
MEDICAL TREATMENT
MEDICAL TREATMENT

Table 1 – Medications used at the point of referral.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total cohort (N = 278)</th>
<th>Primary dystonia (N = 30)</th>
<th>Secondary dystonia (N = 200)</th>
<th>Heredodegenerative dystonia (N = 29)</th>
<th>Primary-plus dystonia (N = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baclofen</td>
<td>118</td>
<td>6</td>
<td>97</td>
<td>13</td>
<td>1</td>
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<tr>
<td>Trihexyphenidyl</td>
<td>98</td>
<td>9</td>
<td>76</td>
<td>11</td>
<td>3</td>
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<tr>
<td>Chloral Hydrate</td>
<td>26</td>
<td>4</td>
<td>17</td>
<td>5</td>
<td>1</td>
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<tr>
<td>Diazepam</td>
<td>57</td>
<td>11</td>
<td>7</td>
<td>3</td>
<td>2</td>
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<tr>
<td>i-DOPA</td>
<td>9</td>
<td>14</td>
<td>2</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Nitrazepam</td>
<td>9</td>
<td>0</td>
<td>14</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Clonidine</td>
<td>9</td>
<td>1</td>
<td>7</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Tetrabenazine</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Triclofos</td>
<td>8</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Tizanidine</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>16</td>
<td>0</td>
<td>14</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Globazam</td>
<td>7</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Midazolam</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Amantidine</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

- Baclofen 42.5%
- Trihexyphenidyl 35.3%
- L-DOPA 20.5%
# Dystonia Classification

## Axis I: Clinical Characteristics

<table>
<thead>
<tr>
<th>Associated features</th>
<th>Body distribution</th>
<th>Age of Onset</th>
<th>Temporal pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated / combined with other movement disorders</td>
<td>Focal</td>
<td>Infancy (0-2)</td>
<td>Disease course</td>
</tr>
<tr>
<td>Isolated dystonia</td>
<td>Segmental</td>
<td>Childhood (3-12)</td>
<td>Static</td>
</tr>
<tr>
<td>Combined dystonia</td>
<td>Multifocal</td>
<td>Adolescence (13-20)</td>
<td>Progressive</td>
</tr>
<tr>
<td>Occurrence of other neurological or systemic manifestations</td>
<td>Hemi dystonia</td>
<td>Early adulthood (21-40)</td>
<td>Temporal variability</td>
</tr>
<tr>
<td></td>
<td>Generalized</td>
<td>Late adulthood (&gt;40)</td>
<td>Persistent Action-specific Diurnal Paroxysmal</td>
</tr>
</tbody>
</table>

Albanese, 2013
CLASSIFICATION AXIS II-ETIOLOGY

A. Nervous system pathology
   - Evidence of degeneration
   - Evidence structural (often static) lesions
   - No degeneration or structural lesion

B. Inherited or acquired
   Inherited
   - Autosomal dominant
   - Autosomal recessive
   - X-linked recessive
   - Mitochondrial

C. Idiopathic
   - Sporadic
   - Familial

Acquired
   - Perinatal brain injury
   - Infection
   - Drug
   - Toxic
   - Vascular
   - Neoplastic
   - Brain injury
   - Psychogenic

Table 7: Causes of Secondary Dystonia in Children

Heredodegenerative Disorders
- Ataxia telangiectasia
- Gangliosidosis
- Glutaric aciduria
- Huntington disease
- Lesch–Nyham disease
- Metachromatic leukodystrophy
- Methylmalonic acidemia
- Mitochondrial disorders
- Niemann–Pick type C
- Pantothenate kinase-associated neurodegeneration (PKAN)*
- Wilson disease

Drugs/Toxins (see Table 8)

Psychogenic

Structural Brain Lesions
- Acute disseminated encephalomyelitis
- Infarction
- Perinatal hypoxia–ischemia
- Stroke
- Tumor

*Also known as Hallervorden-Spatz syndrome
DEEP BRAIN STIMULATION IN DYSTONIA

- Following ablative surgeries (thalamotomy, pallidotomy)
- Following DBS in adults for PD (suppression of dyskinesia in the GPi) and ET
- 1996: 1\textsuperscript{st} child with isolated generalized dystonia receiving GPi DBS in Montpellier (Coubes, 1999 Neurochirurgie)
- Simultaneously, DBS proposed for other forms of dystonia in adults Kumar, Neurology, 1999, and Krauss, Lancet, 1999
THE CASE OF SOPHIE-first patient with DBS treated childhood onset generalized dystonia

« Although her future remains uncertain, we believe that chronic bilateral pallidal stimulation may prove to be the treatment of choice for early onset generalized dystonia, especially in children. Electrical stimulation is a conservative, adaptable, reversible neurosurgical procedure, and seems particularly worthwhile in children because of their ongoing brain development »

Coubes, Neurochirurgie, 1999

21 years of follow-up with DBS
At anesthetic release, involuntary movements are much less severe, no pain, breathing is autonomous.

Recovery is very progressive.

Oral feeding is again possible and PEG tube is removed one month after DBS onset.

IPG early depleted, with recurrence of symptoms, controlled within one week after IPG replacement.

No immediate effect on dystonic symptoms.

It could be possible to propose this therapy also to severe forms of secondary dystonias.

*Coubes, Neurochirurgie, 1999*
SUPERIOR INITIAL RESULTS IN PEDIATRIC ISOLATED DYSTONIA VERSUS ADULTS (AGE AT DBS ADMINISTRATION)

Coubes et al, JNS 2004

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>Preop Value</th>
<th>3 Mos</th>
<th>6 Mos</th>
<th>1 Yr</th>
<th>2 Yrs</th>
<th>p Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>all (31 patients)</td>
<td>59.1 ± 26.4</td>
<td>17.7 ± 20.0</td>
<td>15.3 ± 15.6</td>
<td>12.6 ± 14.0</td>
<td>12.9 ± 13.2</td>
<td>—</td>
</tr>
<tr>
<td>score</td>
<td>72.0 ± 24.9</td>
<td>74.8 ± 21.2</td>
<td>78.6 ± 23.1</td>
<td>79.0 ± 19.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% improvement</td>
<td>62.6 ± 26.1</td>
<td>20.7 ± 27.3</td>
<td>12.8 ± 17.2</td>
<td>9.9 ± 14.4</td>
<td>12.4 ± 15.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DYT1-positive (14 patients)</td>
<td>56.3 ± 27.1</td>
<td>15.6 ± 11.7</td>
<td>17.4 ± 14.4</td>
<td>14.9 ± 13.7</td>
<td>13.4 ± 12.0</td>
<td>0.0002</td>
</tr>
<tr>
<td>score</td>
<td>71.8 ± 15.6</td>
<td>68.6 ± 21.3</td>
<td>73.7 ± 24.0</td>
<td>75.8 ± 20.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% improvement</td>
<td>57.9 ± 28.5</td>
<td>24.2 ± 23.5</td>
<td>21.5 ± 18.8</td>
<td>18.9 ± 17.1</td>
<td>18.9 ± 17.3</td>
<td>0.0003</td>
</tr>
<tr>
<td>adults (12 patients)</td>
<td>59.8 ± 25.8</td>
<td>13.5 ± 16.9</td>
<td>11.4 ± 12.2</td>
<td>8.7 ± 10.4</td>
<td>9.2 ± 8.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>score</td>
<td>78.4 ± 25.8</td>
<td>81.9 ± 14.3</td>
<td>84.8 ± 17.6</td>
<td>84.7 ± 13.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>% improvement</td>
<td>62.0 ± 20.4</td>
<td>63.6 ± 25.8</td>
<td>68.7 ± 27.7</td>
<td>70.1 ± 23.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TARGETS

POSTERO-LATERAL AND VENTRAL PART OF THE GPI

ALTERNATIVE TARGETS FOR DBS IN DYSTONIA

**STN**
When GPi structurally impaired
*PKAN, Ge, 2011*

To avoid side effects related to GPi DBS;
*Kleiner Fisman, 2007; Ostrem, 2011; Blahak, 2011; Ostrem 2017*

**Thalamic motor nuclei**
+**Vim**
Dystonic tremor
*Carvalho, 2013*

Myoclonus dystonia
*Grüber, 2010*

**DYT6 dystonia**
*Mure H, 2014*
+**Ventral lateral anterior (VLa) nucleus**
INDICATIONS

- Medical therapy refractoriness
- Symptoms severe enough to produce disability
- Pain
  
  *Moro et al., 2013*

- Better response in the hyperkinetic forms (but not always)
- Better response in children (in isolated cases) *Vidailhet, 2013*

But most frequently dystonia in children is acquired/degenerative (and complexe...)
INDICATIONS

- No validated criteria for DBS in children (severity, refractoriness to conventional therapy...)

- No cut-off related to symptom severity

- No predictor such as levodopa challenge in PD

- Challenging task especially in acquired /progressive dystonias
INDICATIONS

ISOLATED (PRIMARY) DYSTONIA
- positive outcome in pediatric and adult populations
- DYT1 dystonia (TOR1A gene)
- DYT6 (THAP1 gene)
- Other forms of idiopathic dystonia

COMBINED DYSTONIA
- DYT11 (epsilon sarcoglycan gene) myoclonus dystonia
THAP1 GENE RELATED DYT6 DYSTONIA

- Generalized dystonia and dyskinesia
- Severe axial symptoms (neck, trunk)
- Dysarthria, oromandibular dystonia
- Spread of the symptoms

Decrease of dystonia at early FU (32%; p = 0.046) and 42% at late follow-up.

The rate of responders considerably lower in DYT6 vs DYT1 (57% vs >90%; p = 0.017)

Brüggemann, 2015
COMBINED DYSTONIA DYT11 MYOCLONUS DYSTONIA

- Epsilon sarcoglycane gene related

Myoclonus-dystonia

Myoclonus and dystonia improvement >80%

Pediatric cases

ACQUIRED DYSTONIA

- Dyskinetic/dystonic cerebral palsy; Hemidystonia (post traumatic, vascular)

Two different phenotypes of HIE related CP

First - delayed onset dystonic/dyskinetic CP-very good outcome

Second case-dyskinetic CP; axial decreased tone; mild response to DBS
PROGRESSIVE FORMS
(EVIDENCE FOR DEGENERATION)

- Pantothenate kinase associated neurodegeneration, PANK2 gene mutations
  Castelnau, 2005; Krause M, 2006

- Atypical PLA2G6-neurodegeneration
  (PLAN)
  Cif, 2014
EMERGENCIES

- GNAO1 gene related dystonia/chorea
  
  *Waak, M, 2017*
SPECIFICITIES OF PROGRAMMING IN CHILDREN WITH DYSTONIA

- Clinical improvement not immediate (vs tremor)
- Monotonic time course of improvement (days, weeks, months)
- Often monopolar stimulation (in our experience most frequently double monopolar)
- High frequency stimulation (almost exclusively)
- But settings no different from adults
MANAGEMENT OF PEDIATRIC VS. ADULT DYSTONIA POPULATIONS

- More often generalized anesthaesia suitable/requested
- Higher risk for clinical worsening despite ongoing efficient DBS
- Without efficient treatment, higher risk of life threatening conditions
- Possible influence on growth and development
- Rechargeable systems suitable
PROGNOSIS

- Related to the underlying disorder
- Usual good maintenance of the clinical benefit on long term in isolated and combined dystonias
- However some variability (initial and long term clinical benefit)
- Bradykinesia/gait impairment induced versus control of dystonia/dysphagia
- Rebound at DBS interruption in some patients
- Disease progression
- Tolerance in some patients  
  
  Miyagi, 2013-Two DYT1 cases
RISK RELATED TO DBS: OPERATE LATE

- Status Dystonicus in a case of fast progression of dystonic symptoms (delayed DBS indication)
- Spontaneous femoral fracture because of dystonic spasms
RISK RELATED TO DBS: DISCONTINUE TREATMENT BECAUSE OF NON AVAILABILITY

- Severe worsening of dystonia because of IPG depletion in a patient coming from abroad (no possibility of IPG to be replaced in the Country and no financial support for doing it)
- Disease can become an emergency
RISK RELATED TO DBS: NOT CONTROLLING ALL THE TARGETED SYMPTOMS: DYSPHONIA

THAP1 gene related (DYT6) dystonia: excellent control of cervical and trunk dystonia but no improvement of laryngeal dystonia
COMPLICATIONS

- Surgical site infections 10.3% for new implants and revisions
- Malfunction in 7.7%
- Short extension 3.8%
- Electrode migration in 2.3%
- Skin erosions (2.3%)
- Bleeding (1 patient)
- Unexpected switching off in 18.7% of Soletra/Kinetra and 3.4% of Activa RC,
- Transient seroma at IPG site in postoperative period (8%)

N= 129 patients; mean FU =3.3y

Kaminska, 2017
WHEN TO OPERATE?

- Childhood onset TOR1A gene related DYT1 dystonia
- Surgery in adulthood; excellent control of dystonia but severe scoliosis requesting arthrodesis
RELATIONSHIP BETWEEN ETIOLOGY, SYMPTOM DURATION AND PROGRESSION OF MUSCULOSKELETAL DEFORMITY
RUNNING FAST INTO STATUS DYSTONICUS

- Dystonic storm (independently of the etiology)
- TOR1A gene related DYT1 dystonia
- DBS scheduled; Status Dystonicus two day previous to planned DBS

- Monitor evolution and ANTICIPATE when needed
FREQUENT FAILURES

- Complexe forms (dystonia associated with pyramidal signs, ataxia, ...)
- Mitochondrial encephalopathy (frequently but not always)
- Other Progressive disorders (glutaric aciduria type 1...)
- Static forms with severe structural alterations (thalamic, motor cortex)
- DYT12 rapid onset dystonia parkinsonism
FACTORS OF GOOD PROGNOSIS

- phasic component of dystonia
- short disease duration
- absence of skeletal deformities
- DYT1 gene mutation in isolated dystonia
- no associated weakness and spasticity in acquired forms

*Isaias, 2008, Vasques, 2009, Cif, 2017*
CONCLUSIONS

- DBS in pediatric movement disorders refers mainly to dystonia
- Objective depends on the type of dystonia (etiology and phenotype)
- Objective must be defined and validated together with the child and his family
- Complications are related mainly to DBS system and treatment interruption
- DBS is a life time treatment dealing sometimes with progressive disorders (inform patient and family)
CONCLUSION

DBS administration in pediatrics requires a multidisciplinary team to

- select candidates
- identify reasonable target symptoms
- perform the procedure
- cope with complications related to therapy and devices
- optimize DBS administration
- support the patients and families over the changing life
University Hospital in Montpellier

Over the last 20 years...

Neurology/Pediatric Neurology
L. Cif, V Gonzalez, I de Antonio, M Azais, B Biolsi, A Roubertie, B Echenne, F Rivier

Neurosurgery

P Coubes, S Gil Robles, H Elfertit, T Roujeau, S James, E Chan Seng

ICU: A Boularan, F Gréco, G Cambonie, C Milési

Psychiatry: A Seychelle, A Ionita, D Capdevielle, F Cyprien

Neuropsychology: E Sanrey

Genetics: C Coubes, G Collod-Beroud, M Claustres

Rehabilitation: I Laffont, F Coroian, V Carre, C Jourdan