Diagnostic and therapeutic approach to patients with dystonia

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Phenomenology and Classification of Dystonia: A Consensus Update

Alberto Albanese, MD, Kailash Bhatia, MD, FRCP, Susan B. Bressman, MD, Mahlon R. DeLong, MD, Stanley Fahn, MD, Victor S.C. Fung, PhD, FRACP, Mark Hallett, MD, Joseph Jankovic, MD, Hyder A. Jinnah, PhD, Christine Klein, MD, Anthony E. Lang, MD, Jonathan W. Mink, MD, PhD, Jan K. Teller, PhD

- Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
- Dystonic movements are typically patterned and twisting, and may be tremulous.
- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

Albanese 2013
Movement disorder?

- Hypokinetic (parkinsonism)
  - Simple jerky movements
    - Rythmic: Tremor
    - Nonrythmic: Myoclonus
  - Tics
    - Rythmic: Myoclonus
    - Nonrythmic: Myoclonus

- Hyperkinetic
  - Complex movements/postures
    - Unpredictable: Chorea
    - Predictable/patterned: Dystonia
Differential diagnosis of hyperkinetic (rare) movement disorders

• 1. Phenomenology

• 2. Syndromological associations

• 3. Additional imaging/laboratory/genetic examinations
Phenomenology of dystonia

- Fixed dystonia
- Mobile dystonia
- Dystonic tremor/myoclonus
- Geste antagoniste
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Axis I: Clinical characteristics

I. Clinical characteristics
   I. Age of onset
   II. Body distribution
   III. Progression in time
      I. Disease course
      II. Variability

II. Associated features
   I. Dystonia isolated or combined with another movement disorder
   II. Other neurological or systemic disorders

Axis II: Etiology

I. Pathology of nervous system
   I. Proof of degeneration
   II. Proof of structural (often static) lesion
   III. Without proof of degeneration or structural lesion

II. Inherited or acquired disorder
   I. Inherited
   II. Acquired
   III. Idiopathic
According to age of onset

I. Infant (<2 years)

II. Childhood (3-12 years)

III. Adolescence (13-20 years)

IV. Younger adulthood (21-40 years)

V. Older adulthood (>40 years)
According to body distribution

- Focal – one muscle group or body segment
- Segmental – 2 neighbouring muscle groups or body segments (e.g. head+neck)
- Multifocal – 2 non-neighbouring muscle groups / body parts (e.g. neck + lower limb)
- Hemidystonia
- Generalized – affection of most or all body segments
Temporal pattern

I. Disease course
   I. Static
   II. Progressive

II. Variability
   I. Persistent symptoms
   II. Action-specific
   III. Diurnal fluctuations
   IV. Paroxysmal dystonia
Dopa-responsive dystonia—clinical and genetic heterogeneity

Subhashie Wijemanne & Joseph Jankovic
Published online 23 June 2015
<table>
<thead>
<tr>
<th><strong>Inheritance</strong></th>
<th><strong>Response to L-dopa</strong></th>
<th><strong>Dyskinesia</strong></th>
<th><strong>Other symptoms</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>GTP-cyklohydrolase 1 deficiency</td>
<td>AD</td>
<td>Excellent and persistent</td>
<td>Rare</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>Good, but high doses necessary</td>
<td>Rare</td>
</tr>
<tr>
<td>Tyrosine hydroxylase deficiency</td>
<td>AR</td>
<td>Good but can be incomplete</td>
<td>Frequent</td>
</tr>
<tr>
<td>Sepiapterine reductase deficiency</td>
<td>AR</td>
<td>Good but can be incomplete</td>
<td>Possible</td>
</tr>
<tr>
<td>PTP synthase deficiency</td>
<td>AR</td>
<td>Excellent and persistent</td>
<td>None</td>
</tr>
</tbody>
</table>

Basically all subtypes
- Lower limb onset, generalize, diurnal fluctuations

Wijemmanne Nat Rev Neurology 2015
How to treat dopa-responsive dystonia

<table>
<thead>
<tr>
<th><strong>Initial doses of L-dopa</strong></th>
<th>0.5-1.0 mg/kg/day divided into 3-6 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increasing of L-dopa</strong></td>
<td>by 0.1-0.5 mg/kg/day according to tolerance</td>
</tr>
</tbody>
</table>
| **Management of dyskinesias** | • Decrease L-dopa to last tolerated dose  
|                              | • Delay further increases of dose until dyskinesia disappear  
|                              | • Increase frequency of dosing |
| **Amantadine**              | If abovementioned points not effective |
| **Doses of amantadine**     | 4-6 mg/kg/day |
| **Chronic doses of L-dopa** | 3-20 mg/kg/day according to tolerance |
| **Dopamine agonists**       | If L-dopa not tolerated or does not provide sufficient clinical benefit |
• Paroxysmal kinesigenic dystonia (PKD)
• Paroxysmal non-kinesigenic dystonia (PNKD)
• **Paroxysmal exercise-induced dystonia (PED)**
• Often normal neurological finding between attacks
• Non-epileptic
The Clinical Syndrome of Paroxysmal Exercise-Induced Dystonia: Diagnostic Outcomes and an Algorithm

Roberto Erro, MD,1,2,* Maria Stamoulou, MD, PhD,1,3,4 Christos Ganos, MD,1,5,6 Matej Skorvanek, MD,7,8 Vladimir Han, MD,7,8 Amit Batla, MD, PhD,1 Kailash P. Bhatia MD, FCRP1,*

PED → MRI
Abnormal → Symptomatic PED
Normal → Onset Age

Childhood Early Adulthood → CSF investigations *

Low CSF-serum glucose ratio or low CSF glucose value (<10th percentile) with normal lactate → GLUT-1 (requires testing for the SLC2A1 gene) → Ketogenic diet

Low BH4, HVA, HIAA → DRD (requires testing for the GCH1 gene) → Empirical management (Levodopa, Botulinum toxin, Clonazepam, AEs may be tried)

Normal → DaT-Scan → Abnormal → PD (further genetic testing for early onset PD genes may be pursued)

Normal → Unknown → Anti-parkinsonian drugs (dopaminergic or anti-cholinergic drugs may be tried according to the clinical judgment)
Associated features

• Dystonia isolated or associated with other movement disorder

Dystonia + myoclonus  Dystonia + parkinsonism
<table>
<thead>
<tr>
<th>Dystonia + marked orobulbar involvement</th>
<th>Dystonia + peripheral neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-induced (neuroleptics, antiemetics)</td>
<td>Niemann-Pick type C</td>
</tr>
<tr>
<td>PKAN (PANK2 mutations)</td>
<td>Metachromatic leukodystrophy</td>
</tr>
<tr>
<td>PLAN (PLA2G6 mutations)</td>
<td>Friedreich’s ataxia</td>
</tr>
<tr>
<td>Choreo-akantocasis</td>
<td>Ataxia teleangiectasia</td>
</tr>
<tr>
<td>Neuroferritinopathy</td>
<td>Spinocerebellar ataxies (esp. type 2/3)</td>
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<tr>
<td>Lesch-Nyhan syndrome</td>
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<thead>
<tr>
<th>Dystonia + oculomotor abnormalities</th>
<th>Dystonia + retinitis pigmentosa</th>
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</thead>
<tbody>
<tr>
<td>Niemann-Pick type C</td>
<td>PKAN</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>GM2 gangliozidosis</td>
</tr>
<tr>
<td>Ataxia teleangiectasia, AOA1, AOA2</td>
<td>Metachromatic leukodystrophy</td>
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</tbody>
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<tr>
<th>Dystonia + deafness</th>
<th>Dystonia + progressive dementia</th>
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<tr>
<td>Mitochondrial disorders</td>
<td>GM1 a GM2 gangliozidosis</td>
</tr>
<tr>
<td>Mohr-Tranebjaerg syndrome</td>
<td>Glutaric aciduria</td>
</tr>
<tr>
<td>Woodhouse-Sakati syndrome</td>
<td>Huntington’s disease</td>
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<td></td>
<td>Huntington phenocopies</td>
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Schneider et al. 2010
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   3. Idiopathic
One phenotype many genes

- DYT6 (THAP1 gene)
- DYT24 (ANO3 gene)
- Other genes
One gene many phenotypes
Drug-induced dystonia (acute/tardive)

- Neuroleptics (antiemetics)
  - Therapy anticholinergics (biperiden) i.v.
- Antimalarics, late complications of L-dopa, dopamine agonists
- After overdosing - carbamazepine, fenytoin
- No safe neuroleptics, no safe dosis, no safe period of exposition
- Low rate of remission even after discontinuation
Cerebral palsy

• Overdiagnosed + often an escape diagnosis!
  – No more examinations needed, no specific treatment available...

• Prenatal and perinatal period!
  – Even if perinatal problems - still can have metabolic, mitochondrial or other disorder

• Many patients if properly diagnosed can have a treatable condition
Treatable Inherited Rare Movement Disorders

H. A. Jinnah, MD, PhD, Alberto Albanese, MD, Kailash P. Bhatia, MD, Francisco Cardoso, MD, Gustavo Da Prat, MD, Tom J. de Koning, MD, PhD, Alberto J. Espay, MD, Victor Fung, PhD, FRACP

- **Reduction of toxic products** – Cerebrotendinous xanthomatosis, Dystonia/parkinsonism with manganese accumulation, Gaucher disease, Niemann Pick type C, Wilson disease
- **Dietary interventions** – Abetalipoproteinemia, Cerebral creatine def, GLUT-1 def, Glutaric aciduria type 1, Homocystinuria, Maple syrup urine disease, Methylmalonic aciduria, Phenylketonuria, Propionic acidemia, Pyruvate dehydrogenase complex def, Refsum disease
- **Vitamin supplements** – Abetalipoproteinemia, AADC def, Ataxia with vit E def, Biotin-thiamin responsive basal ganglia disease, Biotinidase def, Cerebral folate def, Cobalamin def, Coenzyme Q10 def, Homocystinuria, Pyruvate dehydrogenase complex def
- **Trigger avoidance** – Alternating hemiplegia of childhood, Biotin-thiamin responsive basal ganglia disease, Episodic ataxia type 2, Glutaric aciduria type 1, Maple syrup urine disease, Methylmalonic aciduria, Paroxysmal kinesigenic / nonkinesigenic dyskinesia, Propionic acidemia, Rapid onset dystonia parkinsonism
- **Specific drugs** – AADC drugs, Dopa-responsive dystonia, Episodic ataxia type 2, GLUT-1 deficiency, Molybdenum cofactor deficiency, Paroxysmal kinesigenic dyskinesia
Therapy algorithm for dystonia

Dystonia

Generalized
- Pharmacological therapy
  - Levodopa
  - Anticholinergics
  - Benzodiazepines, Baclofen, Tetrabenazine

Focal and segmental
- Botulinum toxin for focal symptoms
- Botulinum toxin type A
- Botulinum toxin type B if resistance
- Consider deep brain stimulation

Consider deep brain stimulation
Management of dystonia in Europe: a survey of the European network for the study of the dystonia syndromes


Clinical Practice: Evidence-Based Recommendations for the Treatment of Cervical Dystonia with Botulinum Toxin

Maria Fiorella Contarino¹,²,*, Joost Van Den Doo²⁴, Yacov Balash⁵,⁶, Kailash Bhatia⁷, Nir Giladi⁵,⁶, Johannes H. Koelman⁸, Annemette Lokkegaard⁹, Maria J. Marti¹⁰, Miranda Postma⁸, Maja Relja¹¹, Matej Skovranek¹²,¹³, Johannes D. Speelman⁸, Evelien Zoons⁸, Joaquim J. Ferreira¹⁴, Marie Vidalhét¹⁵,¹⁶,¹⁷,¹⁸,¹⁹, Alberto Albanese²⁰,²¹ and Marina A. J. Tijssen³³
Factors of DBS success

- Selection of appropriate candidates!!!
- Precise placement of electrodes
Bilateral Deep-Brain Stimulation of the Globus Pallidus in Primary Generalized Dystonia

Marie Vidailhet, M.D., Ph.D., Laurent Vercueil, M.D., Jean-Luc Houeto, M.D., Ph.D., Pierre Krystkowiak, M.D., Alim-Louis Benabid, M.D., Ph.D., Philippe Cornu, M.D., Christelle Lagrange, Ph.D., Sophie Tézenas du Montcel, M.D., Ph.D., Didier Dormont, M.D., Ph.D., Sylvie Grand, M.D., Ph.D., Serge Blond, M.D., Olivier Detante, M.D., Bernard Pillon, Ph.D., Claire Ardouin, Ph.D., Yves Agid, M.D., Ph.D., Alain Destée, M.D., and Pierre Pollak, M.D., Ph.D., for the French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group

Pallidal Deep-Brain Stimulation in Primary Generalized or Segmental Dystonia

Andreas Kupsch, M.D., Reiner Benecke, M.D., Jörg Müller, M.D., Thomas Trottenberg, M.D., Gerd-Helge Schneider, M.D., Werner Poewe, M.D., Wilhelm Eisner, M.D., Alexander Wolters, M.D., Jan-Uwe Müller, M.D., Günther Deuschl, M.D., Marcus O. Pinsker, M.D., Inger Marie Skogseid, M.D., Geir Ketil Roeste, M.D., Juliane Vollmer-Haase, M.D., Angela Brentrup, M.D., Martin Krause, M.D., Volker Tronnier, M.D., Alfons Schnitzler, M.D., Jürgen Voges, M.D., Guido Nikkhah, M.D., Ph.D., Jan Vesper, M.D., Markus Naumann, M.D., and Jens Volkman, M.D., for the Deep-Brain Stimulation for Dystonia Study Group
DBS for dystonia

• Isolated generalized dystonia  
  Vidailhet 2005; Kupsch 2006; Bronte-Stewart et al, Mov Disord 2011

• Myoclonus dystonia  
  Cif et al, Mov Disord 2004

• Cervical dystonia / Meige syndrome refractory to BoNT  
  Ostrem et al, Mov Disord 2007

• Selected secondary dystonias
  
  – X-linked parkinsonism-dystonia DYT3 (Lubag)  
    Evidente et al, Mov Disord 2010
  
  – PKAN  
    Timmermann et al, Brain 2010
  
  – Cerebral palsy without cognitive deficit and only mild spasticity  
    Vidailhet et al, Lancet Neurol 2009
  
  – Tardive dystonia  
    Trottenberg 2001
DBS for dystonia

- Isolated > Combined
- Mobile > Fixed
- No MRI abnormalities > MRI structural changes
- Axial > Limb
- Shorter > Longer duration (> fixed skeletal deformities)
DBS in status dystonicus

• Potentially life threatening situation, variable outcomes

• ICU management, sedation, ventilation?, usually pharmacotherapy as first line (benzodiazepines, propofol, barbiturates, anticholinergics, neuroleptics, levodopa, intrathecal morphine, intrathecal baclofen) Fasano, Mov Disord 2012

• In refractory cases acute DBS should be considered
  – Good results shown in DYT1, DYT6, PKAN, tardive dystonia, etc
DBS in myoclonus dystonia

- **GPi > VIM**
  - Myoclonus 75.7% vs. 70.4%
  - Dystonia 60.2% vs 33.3%

Andrews 2010; Rughani 2013

- **worsening of psychiatric symptoms?**

Contarino 2011
DBS in hyperkinetic cerebral palsy

• In selected patients improvement of dystonia 24-49.5% (BFMDRS-m)

  Vidailhet Lancet Neurol 2009; Keen J Neurosurg Ped 2014; Marks J Child Neurol 2013; Romito Eur J Neurol 2015;

• Inclusion criteria
  – Neonatal hypoxic or ischaemic encephalopathy, delayed milestones
  – No other cause of dystonia including metabolic and genetic disorders, focal vascular lesions, head trauma, neuroleptic treatment
  – Little or no spasticity (Ashworth scale <2 for each segment)
  – No more than slight abnormalities seen on T1 MRI images
  – No psychiatric disorders
  – Little or no cognitive impairment
  – Optimised treatment (tried highest tolerated doses of levodopa and anticholinergics)
DBS for PD-related dystonia

- dystonia responsive to levodopa?
- dystonia present only in OFF state?

*Camptocormia*
- Improvement 34.6-78.2%
- Both STN and Gpi used
- Better if shorter duration (<1.5 years)

*Pisa syndrome*
- DBS generally less effective

Umemura 2010; Schulz-Schaeffer 2015; Chieng 2015
DBS for tardive dystonia

- 80+ patients reported (4pts STN, other Gpi)
- Mean improvement 74% on motor score of BFMDRS
- Usually rapid improvement (days – weeks) phasic > tonic movement
- Long-term good effect of stimulation
- Very good cognitive and psychiatric tolerability (1pt worsening of depression, 1pt worsening of psychosis)

Welter 2010; Mentzel 2012; Pouclet-Courtemanche 2016; Sobstyl 2016
Side-effects of Gpi DBS

• Hardware and surgery related

• Stimulation related
  – Especially dysarthria
  – Occasionally hypokinetic gait disorder with freezing of gait
    • Stimulation dependant
Other targets

- STN DBS for dystonia associated with PD (off dystonia with good response to levodopa)

- STN for focal, segmental and generalized isolated dystonia
  - comparable results with Gpi stimulation in a limited number of studies
  - Without neuropsychiatric and cognitive side effects seen in PD
    Ostrem 2011; Schjerling 2013, Mills 2015

- VIM/subthalamic area for dystonic tremor
  Fasano 2014; Pauls 2014

- VIM for Myoclonus dystonia
2nd Kosice Course of Movement Disorders
17. - 19. 5. 2018, Double Tree by Hilton, Košice

www.expy-ke.sk

www.movementdisorders.org

Chorea and Related Disorders
MDS / Education / Conferences & Courses / Upcoming Education Courses / Chorea and Related Disorders

Poznan, Poland
May 25-26, 2018