The Approach to Patients with Dystonia

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Disclosures

● Grant funding (active)
  
  *NIH: U54 NS116025, R01 NS109242
  *Private foundations: Cure Dystonia Now
  *Industry: Retrophin, Revance

● Professional societies
  
  *International Parkinson and Movement Disorders

● Consulting
  
  *Allergan, Bridge Bio, Cavion, CoA Rx, Ipsen, Retrophin, Revance
Learning Objectives

● Describe what is dystonia

● Describe how the many different types of dystonia are grouped and classified

● Summarize basic treatment strategies for the dystonias
Oppenheim’s Historical Concept
The basic defect is a problem with muscle tone

“Dys - Tonia”

abnormal  muscle tone
Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both.

Dystonic movements are typically patterned, twisting, and may be tremulous.

Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.
Dystonia: Key Clinical Features

- Characteristics of muscle contractions
  - slow and sustained
  - rapid and intermittent
  - patterned

- Other helpful features
  - overflow to nearby muscles
  - triggered or worsened by voluntary action
  - geste antagoniste (sensory trick)
Distinguishing Dystonia from related movement disorders

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Dystonia</th>
<th>Chorea</th>
<th>Athetosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustained muscle contractions</td>
<td>often</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Movements worse with action</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Movements are patterned</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Movement speed</td>
<td>slow or fast</td>
<td>medium to fast</td>
<td>slow to medium</td>
</tr>
<tr>
<td>Movements appear flowing</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Overflow to extraneous muscles</td>
<td>yes</td>
<td>sometimes</td>
<td>no</td>
</tr>
<tr>
<td>Geste antagoniste</td>
<td>often</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>
Distinguishing Dystonia from related hyper-tonias

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Dystonia</th>
<th>Spasticity</th>
<th>Rigidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle tone increases with voluntary action</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Muscle tone decreases at rest</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Rate-dependent increase in muscle tone with passive movement</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Muscle tone is greater in extensors than flexors</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Other helpful features</td>
<td>geste antagoniste</td>
<td>corticospinal signs</td>
<td>cogwheeling</td>
</tr>
</tbody>
</table>
Classification of the Dystonias

● Axis I: Clinical features
  *body distribution*: focal, segmental, multifocal, generalized
  *age at onset*: infancy, childhood, adolescence, adult
  *temporal aspects*: progression and/or variability over time
  *associated features*: isolated (pure), combined

● Axis II: Etiology
  *inheritance*: inherited, acquired, idiopathic
  *neuropathology*: static lesion, degenerative, none
Using the Classification System for Clinical Diagnosis

Is it dystonia?

- isolated dystonia
  - movement signs
    - parkinsonism
    - myoclonus
    - ataxia
    - etc...

- combined dystonia
  - neurologic signs
    - dementia
    - neuropathy
    - epilepsy
    - etc...
  - systemic signs
    - hematologic
    - endocrine
    - solid organ
    - etc...
Assessment of Patients With Isolated or Combined Dystonia:
An Update on Dystonia Syndromes

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ABSTRACT: The clinical evaluation of a patient with dystonia is a stepwise process, beginning with classification of the phenomenology of the movement disorder(s), then formulation of the dystonia syndrome, which, in turn, leads to a targeted etiological differential diagnosis. In recent years, there have been significant advances in our understanding of the etiological basis of dystonia, aided especially by discoveries in imaging and genetics. In this review, we provide an update on the assessment of a patient with dystonia, including the phenomenology of dystonia and highlighting how to integrate clinical, imaging, blood, and neurophysiological investigations in order to formulate a dystonia syndrome. Evolving or emerging dystonia syndromes are reviewed, and potential etiologies of these as well as established dystonia syndromes listed to guide diagnostic testing.

Using the Classification System for Etiological Diagnosis

~200 different dystonic disorders
18 tables according to associated features
Treatment of the Dystonias

- All dystonias are “treatable”
  - Counseling
  - Physical and occupational therapy
  - Oral medications
  - Botulinum toxins

- Some dystonias have special treatments
  - Mechanism-specific treatments
  - Empirically discovered useful treatments
# Dystonia Treatment: Oral Medications

<table>
<thead>
<tr>
<th>Treatment class</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergics</td>
<td>benztropine, biperiden, ethopropazine, ophenadrine, procyclidine, trihexyphenidyl</td>
</tr>
<tr>
<td>Dopaminergics</td>
<td>levodopa, deutetabenazine, tetrabenazine, valbenazine</td>
</tr>
<tr>
<td>GABAergics</td>
<td>alprazolam, baclofen, chlordiazepoxide, clonazepam, diazepam</td>
</tr>
<tr>
<td>Muscle relaxers</td>
<td>carisoprodol, chlorzoxazone, cyclobenzaprine, metaxolone, methocarbamol, orphenadrine</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>carbamazepine, cannabidiol, cyproheptadine, gabapentin, lithium, mexiletine, nabilone, riluzole, tizanidine, zolpidem</td>
</tr>
</tbody>
</table>
Dystonia Treatment: Botulinum toxins
# Dystonia Treatment: Botulinum Toxins

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Abo botulinum toxin A</th>
<th>Inco botulinum toxin A</th>
<th>Ona botulinum toxin A</th>
<th>Rima botulinum toxin B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation supplied</td>
<td>freeze dried</td>
<td>powder</td>
<td>vacuum dried</td>
<td>liquid</td>
</tr>
<tr>
<td>Dose sizes</td>
<td>300, 500</td>
<td>50, 100</td>
<td>100, 200</td>
<td>2500, 5000, 10000</td>
</tr>
<tr>
<td>Storage</td>
<td>refrigerate</td>
<td>room temp</td>
<td>refrigerate</td>
<td>refrigerate</td>
</tr>
<tr>
<td>Approximate dose equivalents</td>
<td>2.5 - 3.0</td>
<td>1.0</td>
<td>1.0</td>
<td>40</td>
</tr>
</tbody>
</table>
Dystonia Treatment: Surgery

Deep electrode

Implanted power pack
Dystonia Treatment: Surgery

- Design
  multi-center
  DBS of GPi
  stimulation vs sham (3 months)
  additional un-blinded phase

- Patient Population
  $N = 40$
  generalized or segmental
  20 men, 20 women
  average age: $39 \pm 13 \text{ yrs}$
Dystonia Treatment: Surgery

Randomized Study Period

Three months after randomization, severity scores were significantly lower in the neurostimulation group than in the sham-stimulation group (P<0.001) (Fig. 2A). The movement score improved by a mean of 15.8±14.1 points (a 39.3% reduction in symptoms) in the neurostimulation group, as compared with 1.6±4.0 points (a 4.9% reduction) in the sham-stimulation group (Table 2). In the neurostimulation group, 15 patients fulfilled our criterion of a positive response to treatment (>25% reduction in the movement score), as compared with only 3 patients in the sham-stimulation group.

Likewise, disability scores improved significantly in the neurostimulation group, by a mean of 3.9±2.9 points (a 37.5% reduction in disability), as compared with a mean of 0.8±1.2 points (8.3%) in the sham-stimulation group (Table 2). Neurostimulation was significantly superior on all symptom subscores of the Burke–Fahn–Marsden Dystonia Rating Scale and most of the disability items. Quality of life, as assessed on the basis of the score for the physical component of the SF-36, improved in the neurostimulation group by 10.1±7.4 points (a 29.8% improvement), which differed significantly from the change in the placebo group (3.8±8.4 points, an 11.4% improvement). The effects on primary and secondary outcomes are summarized in Table 2.

Open-Label Study Extension

Among the patients who had been randomly assigned to the sham-stimulation group during the first 3 months, the movement score on the Burke–Fahn–Marsden Dystonia Rating Scale improved by an average of 12.0±10.0 points (36.8%) after 6 months of continuous neurostimulation (Fig. 2B). Among patients originally assigned to receive neurostimulation, the movement score further improved, with a decline from 24.5±22.8 at 3 months to 19.8±15.1 at 6 months, but this additional improvement was not significant (P = 0.24).

A comparison of the outcome measures at baseline and after 6 months of neurostimulation was used to assess the magnitude of the treatment effect in the entire study group (Table 3). All movement symptoms (except for speech and swallowing), all disability scores, the scores on the physical and mental components of the SF-36, and the global clinical assessments showed pronounced and significant improvements among patients in the neurostimulation group. The severity of dystonia as reflected by the movement score decreased by more than 75% in 5 patients, more than 50% in 15 patients.
Algorithm for Diagnosis & Treatment

1. **Age**
   - Late onset
   - Early onset

2. **Examination**
   - Focal
   - Generalized

3. **Diagnostic Testing**
   - All others
   - Special populations

4. **BTX**

5. **Adjunctive Oral Medications**

6. **1st Levodopa**

7. **Mechanism-Specific Treatments**

8. **Neurosurgery**
Dystonias with Special Treatments

Mov Disord 2018

REVIEW

Treatable Inherited Rare Movement Disorders

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for the International Parkinson’s Disease Movement Disorders Society Task Force on Rare Movement Disorders

◆ 30 inherited movement disorders; half with dystonia

Target reduction therapy
Vitamin/cofactor therapy
Avoid triggers
Dietary modifications
Specific drugs
The Dystonias

By H. A. Jinnah, MD, PhD

ABSTRACT

PURPOSE OF REVIEW: This article provides a summary of the state of the art in the diagnosis, classification, etiologies, and treatment of dystonia.

RECENT FINDINGS: Although many different clinical manifestations of dystonia have been recognized for decades, it is only in the past 5 years that a broadly accepted approach has emerged for classifying them into specific subgroups. The new classification system aids clinical recognition and diagnosis by focusing on key clinical features that help distinguish the many subtypes. In the past few years, major advances have been made in the discovery of new genes as well as advances in our understanding of the biological processes involved. These advances have led to major changes in strategies for diagnosis of the inherited dystonias. An emerging trend is to move away from heavy reliance on the phenotype to target diagnostic testing toward a broader approach that involves large gene panels or whole exome sequencing.

SUMMARY: The dystonias are a large family of phenotypically and etiologically diverse disorders. The diagnosis of these disorders depends on clinical recognition of characteristic clinical features. Symptomatic treatments are useful for all forms of dystonia and include oral medications, botulinum toxins, and surgical procedures. Determination of etiology is becoming increasingly important because the number of disorders is growing and more specific and sometimes disease-modifying therapies now exist.

INTRODUCTION

The dystonias are a diverse family of disorders that share an underlying phenomenon of excessive contractions of specific muscle groups leading to abnormal movements. Any region of the body can be affected, and the overt manifestations depend on the severity and distribution of muscles involved. In its mildest forms, abnormalities appear as slight distortions of otherwise normal movements. In patients who are more affected, abnormal movements have a more obvious appearance of cramping, stiffening, jerking, or twisting. The most severe cases of dystonia are associated with fixed abnormal postures or joint deformities with severe disability.

The causes of dystonia are similarly diverse. Some types of dystonia are associated with overt neuropathologic abnormalities of the brain that can be detected by neuroimaging or postmortem histopathologic studies, such as focal lesions or degenerative changes. Some types of dystonia are acquired whereas...
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