Pathophysiology of Dystonia: Translation
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Disclosures

• No conflict of interest
Phenomenology and Classification of Dystonia: A Consensus Update

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New Definition

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.


An ad hoc committee sponsored by Dystonia Medical Research Foundation, The Dystonia Coalition, & The European Dystonia COST Action
(COST = Cooperation in Science and Technology)
Generalized Dystonia

Patient of M. Tagliati
Jerky Cervical Dystonia

Fahn, Jankovic & Hallett 2011
Tremulous Cervical Dystonia

Bhidayasiri & Tarsy 2013
Musician’s Dystonia with Overflow

Patient from NINDS, NIH
New Classification Scheme

- Two axes
  - Clinical Features
    - age at onset, body distribution, temporal pattern, coexistence of other movement disorders, other neurological manifestations
    - Syndromes are clusters of clinical features
  - Etiology
    - Nervous System Pathology
    - Inherited or Acquired
Understanding Dystonia

- Genes
  - Modifiers
- Cell biology
- Regional anatomical abnormality
- Axis One
  - Phenotype
- Pathophysiology
- Network Dysfunction
<table>
<thead>
<tr>
<th>Disease (MIM)</th>
<th>Gene</th>
<th>Locus</th>
<th>Phenotype</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PURE PRIMARY TORSION DYSTONIA</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DYT1 (128100)</td>
<td>TOT1A</td>
<td>9q34</td>
<td>Early-onset generalized limb onset dystonia</td>
<td>AD</td>
</tr>
<tr>
<td>DYT2 (224500)</td>
<td>–</td>
<td>–</td>
<td>Early-onset generalized dystonia with prominent cranio-cervical involvement</td>
<td>AR</td>
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<tr>
<td>DYT4 (128101)</td>
<td>TUBB4a</td>
<td>19p13.12–13</td>
<td>Whispering dysphonia</td>
<td>AD</td>
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<tr>
<td>DYT6 (602629)</td>
<td>THAP1</td>
<td>8p11.21</td>
<td>Generalized cervical and upper-limb-onset dystonia</td>
<td>AD</td>
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<tr>
<td>DYT7 (602124)*</td>
<td>–</td>
<td>18p</td>
<td>Adult-onset cervical dystonia</td>
<td>AD</td>
</tr>
<tr>
<td>DYT11 (607571)</td>
<td>–</td>
<td>1p36.32–p36.13</td>
<td>Cervical and upper-limb dystonia</td>
<td>AD</td>
</tr>
<tr>
<td>DYT17 (612406)</td>
<td>–</td>
<td>20p11.2–q13.12</td>
<td>Segmental or generalized dystonia with prominent dysphonia</td>
<td>AR</td>
</tr>
<tr>
<td>DYT21 (614588)</td>
<td>–</td>
<td>2q14.3–q21.3</td>
<td>Adult-onset generalized or multifocal dystonia, often starting with blepharospasm</td>
<td>AD</td>
</tr>
<tr>
<td>DYT23 (614860)</td>
<td>CZ1</td>
<td>9q34</td>
<td>Adult-onset cervical dystonia</td>
<td>AD</td>
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<tr>
<td>DYT24 (615034)</td>
<td>ANO3</td>
<td>11p14.2</td>
<td>Cranio-cervical dystonia with laryngeal and upper-limb involvement</td>
<td>AD</td>
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<tr>
<td>DYT25 (615073)</td>
<td>GNAL</td>
<td>18p11</td>
<td>Adult-onset cervical dystonia</td>
<td>AD</td>
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<tr>
<td><strong>PRIMARY DYSTONIA-PLUS SYNDROME</strong></td>
<td></td>
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<tr>
<td>DYT5 (218230)</td>
<td>GCH1</td>
<td>14q22.2</td>
<td>Dopa-responsive dystonia</td>
<td>AD</td>
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<tr>
<td>THD (605407)</td>
<td>TH</td>
<td>11p15.5</td>
<td>Dopa-responsive dystonia</td>
<td>AR</td>
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<td>DYT11 (159900)</td>
<td>SGCE</td>
<td>7q21.3</td>
<td>Myoclonus-dystonia</td>
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<tr>
<td>DYT12 (128235)</td>
<td>ATP1A3</td>
<td>19q13.2</td>
<td>Rapid-onset dystonia parkinsonism</td>
<td>AD</td>
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<tr>
<td>DYT15 (607488)</td>
<td>–</td>
<td>18p11</td>
<td>Myoclonus-dystonia</td>
<td>AD</td>
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<tr>
<td>DYT16 (612057)</td>
<td>PRKRA</td>
<td>2q31.2</td>
<td>Early-onset dystonia parkinsonism</td>
<td>AR</td>
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<tr>
<td><strong>PAROXYSMAL SYNDROME</strong></td>
<td></td>
<td></td>
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<tr>
<td>DYT8 (118800)</td>
<td>MR1</td>
<td>2q35</td>
<td>Paroxysmal non-kinesigenic dyskinesia (PNKD)</td>
<td>AD</td>
</tr>
<tr>
<td>DYT9 (601042)/DYT18</td>
<td>SLC2A1</td>
<td>1p34.2</td>
<td>Paroxysmal dyskinesias with episodic ataxia and spasticity/paroxysmal exercise-induced dystonia (PED)</td>
<td>AD</td>
</tr>
<tr>
<td>DYT10 (128200)</td>
<td>PRRT2</td>
<td>16p11.2</td>
<td>Paroxysmal kinesigenic dyskinesia (PKD)</td>
<td>AD</td>
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<tr>
<td>DYT18 (611031)</td>
<td>–</td>
<td>16q13–q22.1</td>
<td>Paroxysmal kinesigenic dyskinesias 2 (PKD2)</td>
<td>AD</td>
</tr>
<tr>
<td>DYT20 (611147)</td>
<td>–</td>
<td>2q31</td>
<td>Paroxysmal non-kinesigenic dyskinesias 2 (PNKD2)</td>
<td>AD</td>
</tr>
<tr>
<td><strong>HEREDODEGENERATIVE DYSTONIA SYNDROME</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DYT3 (314250)</td>
<td>TAF1</td>
<td>Xq13.1</td>
<td>Dystonia parkinsonism</td>
<td>X-R</td>
</tr>
</tbody>
</table>

*AD, autosomal dominant; AR, autosomal recessive; X-R, X-linked recessive. *DYT7 locus on chromosome 18p has been recently questioned (Winter et al., 2012).*
Group difference in RAC binding at rest (A) and its change (mean percentage ?9BP) during symptomatic speech production (B) and asymptomatic sequential finger tapping (C).
Raclopride binding at rest (D2 receptors)

A. Healthy controls (HC)

B. Writer’s Cramp (WC) patients

C. WC patients vs. HC

Dopamine release with tapping

A. Healthy controls (HC)

B. Writer’s Cramp (WC) patients

C. WC patients vs. HC

Translation

• Dopamine can be useful therapy in a number of circumstances
THE ANATOMICAL BASIS OF SYMPTOMATIC HEMIDYSTONIA

V. J. A. OBESO; J. J. ZARRANZ; and A. E. LANG

BY C. D. MARSDEN

TABLE 7. SUMMARY OF DISTRIBUTION OF LESIONS RESPONSIBLE FOR DYSTONIA IN 13 PATIENTS WITH CT SCAN LOCALIZATION AND 7 PATIENTS WITH PATHOLOGY, COMBINED WITH 28 PATIENTS FROM THE PRESENT STUDY

<table>
<thead>
<tr>
<th>Site of dystonia</th>
<th>Thalamus</th>
<th>Caudate nucleus</th>
<th>Lentiform nucleus</th>
<th>Internal capsule</th>
<th>Cortex</th>
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<tbody>
<tr>
<td>Hemidystonia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Arm dystonia</td>
<td>1</td>
<td></td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hand dystonia</td>
<td>1</td>
<td></td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Foot dystonia</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Torticollis</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>16</td>
<td>5</td>
</tr>
</tbody>
</table>

Data in Table 7 combined with Table 4

In particular, the pathology of examination was in the contralateral caudate nucleus, lentiform nucleus, and thalamus in the literature with thalamus or in a combination of these structures. Review of 13 other patients with pathologically discrete hemidystonia and lesions defined by CT scan, and of 7 other patients with dystonia in the literature indicated involvement of these structures. Dystonia may be due to lesions associated with hemidystonia, also indicating involvement of these structures. Lesions in the thalamus itself, or due to abnormal input from thalamus to premotor cortex, due to lesions to the striatum projecting by way of the globus pallidus to the thalamus.
Among all 48 cases, lesions were found in multiple regions including the thalamus (n = 12), lower brainstem (n = 11), basal ganglia (n = 9), cerebellum (n = 9), midbrain (n = 7), and cortex (n = 1).
Voxel Based Morphometry, VBM

Grey-matter increase bilaterally in the putamen in Blepharospasm. Results are projected on (A) coronal and (B) axial slices of the study-specific averaged T1-image in a standard stereotactic space derived from all the 32 study participants.

Etgen, T et al. J Neurol Neurosurg Psychiatry 2006;77:1017-1020
BEB subjects had increased gray matter in the caudate head and cerebellum bilaterally as well as decrease in the putamen and thalamus bilaterally.

Obermann et al. 2007
VBM Study of Focal Hand Dystonia (Garraux et al. 2004)

Increased gray matter in sensory cortex bilaterally
Pathology in DYT1 dystonia: Perinuclear inclusions in midbrain reticular formation and periaqueductal gray (including the PPN)

McNaught et al. 2004
Pathology in DYT1 dystonia: Tau/Ubiquitin staining in SNpc and LC

A-C is LC
D is SNpc
A-B is ubiquitin staining
C-D is tau staining

McNaught et al. 2004
Pathology in DYT1 dystonia: NIH work in progress

Ubiquitin protein conjugate staining of midbrain (3 of 5 cases) AND striatum (5 of 7 cases)
Also some TorsinA staining in both regions…

Ray-Chaudhury, Rahimpour, Tinaz, Edwards, Hallett
Role of the Cerebellum in Dystonia

• Animal models
  – Calderon et al. Nat Neurosci 2011: model of DYT12
  – Raike et al. Neurobiol Dis 2012: limited Purkinje cell lesions produced focal dystonias

• TMS studies

• Cerebellar control of cortical plasticity
  – Hubsch et al. Brain 2013: reduced cerebellar influence on paired-associative stimulation in motor cortex

• Eye blink conditioning
  – Teo et al. JNRP 2009: reduced conditioning
Role of the Cerebellum in Dystonia

- Imaging
  - Structural abnormalities
    - Delmaire et al. Neurology 2007: decreased gray matter
  - Activation abnormalities
    - Niethammer et al. Neurobiol Dis 2011: PET: increase in normal motor-related activation pattern (NMRP)
    - Several studies: fMRI: various (mild) abnormalities
  - Connectivity abnormalities
    - Argyelan et al. J Neurosci 2009
    - Gallea et al. In preparation
Statistical parametric maps demonstrating structural decrease in gray matter between patients with focal hand dystonia and control subjects

Reduced dentatothalamic DTI in DYT1 gene carriers


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Loss of inhibition
  – Demonstrated in many inhibitory networks at spinal, brainstem and cortical levels
  – Surround inhibition is specifically affected
Sensory abnormalities
  – Subtle but definite effects in both spatial and temporal discrimination
Abnormal plasticity
  – “Enhanced” but loss of homeostatic feature
Technique of Paired-Pulse Stimulation
To assess short intracortical inhibition, SICI
(and intracortical facilitation, ICF)

2 ms ISI

Kujirai et al. 1993
Technique of Paired-Pulse Stimulation

Kujirai et al. 1993
Intracortical Inhibition In Dystonia

Ridding et al. 1995

Less inhibition
ICI and ICF in Dystonia

Ridding et al. 1995
Physiology of making selective movement

Inhibited Movements

Desired Movement

Surround Inhibition
Facilitation occurs with reduction of GPi output
Inhibition occurs with increase in GPi output

A center-surround organization of GPi output can sharpen the motor command
Method for Studying Surround Inhibition

1 = rest
2 = premotor
3 = phasic
4 = tonic

Surround Inhibition is absent in Focal Hand Dystonia

Conclude: Overflow seems due to loss of inhibition
SICI in normals is not a mechanism for SI, but it is abnormal in focal hand dystonia

Temporal Discrimination

Tamura et al. Mov Disord 2008;23:558
Influence of a first SEP on a second SEP at various short intervals

*Sensory dysfunction seems also due to loss of inhibition*
Temporal Discrimination Correlates with Loss of Sensory Inhibition

Tamura et al. Mov Disord 2008;23:558
SEP mapping of fingers

Normal

Dystonia

Loss of GABA

• GABA MRS
  – Levy & Hallett 2002
  – Herath et al. 2010

• Flumazenil PET
  – Garibotto et al. 2011
  – Gallea et al. in preparation
    • M1, Putamen, Cerebellum
Lower Flumazenil Binding in FHD in right cerebellum, left sensorimotor cortex, bilateral anterior insula, left dorsal posterior putamen (Gallea et al in preparation).

Flumazenil binds to the GABA-A receptor.
Increasing inhibition with GABAergic agents can be useful therapy in a number of circumstances.

Increasing cortical inhibition with TMS techniques has also shown transient benefit.
Increase of Plasticity
Technique of Paired Associative Stimulation

Test
pre

Interventional paired stimulation

Test
post

90 pairs
ISI 25 ms

2 mV

100 ms

LTP-like plasticity

Stefan et al. 2000 (Classen Laboratory)
Increase in PAS in Dystonia

Quartarone et al 2003
Homeostatic property of motor cortex learning

- Demonstrated by interaction of learning and paired-associative stimulation (PAS)
Translation

- For hand dystonia, at least, it seems that aberrant plasticity triggers the disorder.
- There is some evidence that certain types of motor and sensory training can improve the dystonia (at least transiently).
How is it possible to have a task specific deficit in one hand?

- Basically the hand is fine since it can perform other tasks without difficulty.
- Basically the motor program is fine since it can be carried out by other limbs.
- The difficulty must be in the linkage of task and effector for the particular task.
Signatures with Different Effectors

Right hand

Left hand

Right arm
(large size on board)

Left arm
(large size on board)

Mouth (moving head)

Right foot
Writing with Different Effectors

C. David Marsden writing with right arm, using:

A. Fingers

B. Forearm

C. Shoulder

Marsden CD. The mysterious motor function of the basal ganglia. Neurology 1982
fMRI Experiment

- Purpose: to identify activation relating to effector, activation due to task, and then to look at the combination
- Block design with 9 conditions:
  - 3 effectors: right hand, left hand, right foot
  - 3 tasks: writing, zigzagging, tapping
  - Each effector did each task
- Normal subjects and right handed patients with (right hand) writer’s cramp
Exclusive for Right Hand Writing

Control Subjects

Patients with WC

There is also a specific deficit in the connectivity of the parietal-premotor pathway in FHD

Gallea, Horovitz et al. In preparation
The left putamen is not significantly active with RHw in patients, and less connected to the PMv.

Gallea, Horovitz et al. In preparation
Parietal-Premotor Connections

Rizzolatti et al. 1998
Quantitative comparison of chimpanzee and human activation during transitive grasping observation

Translation

- Dystonia, in the end, is produced by a network abnormality, and the efficacy of DBS in dystonia is likely due to alterations in network function
Non-motor Manifestations

- Sensory abnormalities
  - Mild sensory deficits
  - Pain
- Depression
  - No strong evidence for anxiety
- Sleep impairment
  - Possibly related to depression
- (No cognitive or attention deficit)
- Reduced quality of life
Depression

- Not related to severity of motor disorder
- Some component is likely to be secondary
  - Improvement of mood occurs with successful motor treatment
- Can start prior to motor disorder
Separate basal ganglia loops may give rise to motor and non-motor symptoms

Rodriguez-Oroz et al., Lancet Neurology 2009;8:1128
Resting-state fcMRI

11 Primary Focal Dystonia vs. 10 normal controls

(8F; 63±6)  (5F; 62±6)

Increased FC between dorsal putamen and lingual gyrus (p=0.0002)

Decreased FC between ventral caudate and inferior frontal gyrus (p<0.00001)
Understanding Dystonia

Genes

Modifiers

Dopamine dysregulation
GABA deficiency

Basal Ganglia
Cerebellum
Cortex

Excessive Movement AND the Non-motor Manifestations too

Defective Inhibition and Plasticity

Cortical and Subcortical Network Dysfunction
Save the date!

30th International Congress of Clinical Neurophysiology of the International Federation of Clinical Neurophysiology (IFCN)
21–24 March 2014, Berlin/Germany

58th Annual Meeting of the German Society for Clinical Neurophysiology and Functional Imaging (DGKN)
20–23 March 2014, Berlin/Germany

Conveners
Prof. Otto W. Witte, Jena/Germany
Prof. Reinhard Dengler, Hannover/Germany

www.iccn2014.de