GENETICS AND TREATMENT OF DYSTONIA

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DYSTONIA

Definition:

- abnormal sustained muscle contraction & postures
- may be associated with tremor and/or myoclonic movements
- may be alleviated by sensory tricks
Figure 1 Hierarchical organization of Axis I (clinical characteristics) and Axis II (etiology) of the dystonia classification.
7+ YEARS TO DIAGNOSIS

53% had to use savings

37% borrowed money from family/friends

34% sought help from charity

Average number of misdiagnoses

3 Physicians involved before diagnosis

The Bare Diagnosis: Patient's Road to

89% ANXIETY
65% DEPRESSION
75% STRESS

86% ANXIETY
65% ISOLATION
75% DEPRESSION

PATIENTS

72% DEPRESSION
64% ISOLATION

CAREGIVERS

Reported emotional impact of PD
## Dystonia - Classification

**Primary Dystonia**
- sporadic
- inherited
  - DYT1

**Dystonia – plus syndrome**
- PD, PSP, MSA, CBGD
  - inherited
    - dopa-responsive dystonia (DYT 5)
    - dystonia – myoclonus (DYT 11)
    - Huntington’s disease
    - Wilson’s disease
    - Fahr’s disease

**Secondary Dystonia**
- mitochondrial disorders
- ceroid lipofuscinosis
- hexosaminidase A & B
- hypoparathyroidism
- neurotoxic
  - carbon monoxide, manganese
- head injury
- infectious
- post infectious
- paraneoplastic
- drug induced
- structural
METHODICAL STRATEGY FOR DIAGNOSIS OF DYSTONIA

Diagnosis and Treatment of Dystonia, Jinnah H. A. Neurol Clin. 2015 Feb; 33(1): 77-100
GENETIC TESTING
BUT THE FAMILY HISTORY WAS “NEGATIVE”

• ‘Real life’ reasons:
  • early unrelated deaths
  • diagnoses not shared with rest of family
  • family history not known!
  • wrong diagnosis or phenocopies
  • non-paternity
  • adoption
KARYOTYPE

5-10 Mb

COMPARATIVE GENOMIC HYBRIDIZATION

140 kb

SEQUENCING

1bp
Next Generation Sequencing (NGS)

TARGETED PANELS (group of genes)

WES: Whole EXOME sequencing (protein coding)

Non-TARGETED

WGS: WHOLE GENOME SEQUENCING
GENETICS OF IDIOPATHIC DYSTONIA

• 20% have family history

• autosomal recessive
  • both copies of gene abnormal

• autosomal dominant
  • one copy abnormal

• X-linked
  • boys affected
NOW

• over 200 genes associated with dystonia

• in most - environmental factors in genetically predisposed person
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Phenotype</th>
<th>Mutational spectrum</th>
<th>Protein function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated dystonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DYT-TOR1A</td>
<td>Early-onset generalized dystonia (also known as Oppenheim dystonia or DYT1 dystonia)</td>
<td>In most cases, the same mutation (e.904_906delGAG; p.302delGlu)</td>
<td>ATPases associated with a variety of cellular activities, considered to function as a molecular chaperon</td>
</tr>
<tr>
<td>DYT-THAP1</td>
<td>Adolescent-onset dystonia with mixed phenotype (or DYT6 dystonia)</td>
<td>About 100 different mutations</td>
<td>Transcription factor</td>
</tr>
<tr>
<td>DYT-GNAL</td>
<td>Adult-onset segmental dystonia</td>
<td>About 30 different mutations</td>
<td>Involved in signal transduction</td>
</tr>
<tr>
<td>DYT-ANO3</td>
<td>Late-onset cranio cervical dystonia</td>
<td>Many different mutations, pathogenicity often not clear (no segregation)</td>
<td>Calcium-activated chloride channels</td>
</tr>
<tr>
<td>Combined dystonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DYT-GCH1</td>
<td>Dopa-responsive dystonia (also known as Segawa syndrome or DYT5 dystonia)</td>
<td>More than 100 different mutations</td>
<td>Rate-limiting enzyme in the biosynthesis of tetrahydrobiopterin</td>
</tr>
<tr>
<td>DYT-ATP1A3</td>
<td>Rapid-onset dystonia-parkinsonism (or DYT12 dystonia)</td>
<td>About 20 different mutations</td>
<td>Catalytic subunit of an ionic pump</td>
</tr>
<tr>
<td>DYT-FRKRA</td>
<td>Dystonia-parkinsonism (DYT16)</td>
<td>One confirmed mutation (c.665C &gt; T, p.Pro222Leu)</td>
<td>Protein kinase with function in stress response</td>
</tr>
<tr>
<td>DYT-SGCE</td>
<td>Myoclonus dystonia (DYT11)</td>
<td>About 80 different mutations</td>
<td>Probably transmembrane protein; function largely unknown</td>
</tr>
</tbody>
</table>
TREATMENT
<table>
<thead>
<tr>
<th>Disorder</th>
<th>Typical age at onset</th>
<th>Typical characteristics of dystonia</th>
<th>Other typical clinical features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ataxia with vitamin E deficiency</td>
<td>childhood to early adulthood</td>
<td>rare patients present with dystonia instead of ataxia</td>
<td>ataxia, neuropathy</td>
<td>vitamin E supplementation</td>
</tr>
<tr>
<td>Autoimmune movement disorders</td>
<td>any age</td>
<td>focal or generalized dystonia</td>
<td>systemic signs of autoimmune disease</td>
<td>treat autoimmune process</td>
</tr>
<tr>
<td>Cerebral creatine deficiency type 3</td>
<td>infancy</td>
<td>generalized dystonia</td>
<td>developmental delay, myopathy</td>
<td>creatine</td>
</tr>
<tr>
<td>Dystonia with brain manganese accumulation</td>
<td>childhood</td>
<td>progressive generalized dystonia</td>
<td>Parkinsonism, liver disease, polycythemia</td>
<td>chelation therapy</td>
</tr>
<tr>
<td>Methylmalonic aciduria</td>
<td>childhood</td>
<td>static generalized dystonia following encephalopathic crisis</td>
<td>developmental delay, encephalopathic crisis, renal insufficiency, pancytopenia</td>
<td>avoid or treat aggressively any intercurrent illness, protein restriction</td>
</tr>
<tr>
<td>Niemann Pick type C</td>
<td>early childhood to early adulthood</td>
<td>progressive generalized dystonia</td>
<td>dementia, ataxia, spasticity, seizures, supranuclear gaze palsy</td>
<td>miglustat</td>
</tr>
<tr>
<td>Rapid onset dystonia-Parkinsonism</td>
<td>early childhood to late adulthood</td>
<td>bulbar or generalized dystonia following encephalopathic crisis</td>
<td>psychomotor disability</td>
<td>avoid or treat aggressively any intercurrent illness, protein restriction</td>
</tr>
</tbody>
</table>

References:
Diagnosis and Treatment of Dystonia, Jinnah H. A. Neurol Clin. 2015 Feb; 33(1): 77-100
MEDICAL TREATMENT OF PRIMARY DYSTONIA

• levodopa
• dopamine agonists
• tetrabenazine
• neuroleptics
  • atypical
  • typical
MEDICAL TREATMENT OF PRIMARY DYSTONIA

• muscle relaxants
  • Baclofen, clonazepam

• anti-epileptics

• others
  • cannabinoids
GENERALIZED DYSTONIA

- levodopa trial
- Marsden Cocktail (high dose anticholinergics, neuroleptic, tetrabenazine)
- botulinum toxin injections supplemental
DEEP BRAIN STIMULATION OF GPI

- Demonstrated long term benefit
- Primary generalized dystonia
- Secondary dystonias
FOCAL DYSTONIAS

- adult onset, non-progressive
- types:
  - blepharospasm
  - cervical
  - oromandibular
  - occupational
BOTULINUM TOXINS

- onabotulinum toxin type A
- abobotulinum toxin type A
- incobotulinum toxin type A
- rimabotulinum toxin type B
## ONABOTULINUM TOXIN A TREATMENT

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Dose range (U)</th>
<th>Mean dose (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical dystonia</td>
<td>70 – 400</td>
<td>222</td>
</tr>
<tr>
<td>Hemifacial spasm</td>
<td>12.5 – 70</td>
<td>29.4</td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>25 – 100</td>
<td>51.5</td>
</tr>
<tr>
<td>Focal / segmental</td>
<td>30 – 300</td>
<td></td>
</tr>
<tr>
<td>Writer’s cramp</td>
<td>30 – 200</td>
<td>77.4</td>
</tr>
<tr>
<td>Meige’s syndrome</td>
<td>70 – 200</td>
<td>110</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>175 – 300</td>
<td>253</td>
</tr>
<tr>
<td>Jaw opening</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Jaw closing</td>
<td>200</td>
<td>200</td>
</tr>
</tbody>
</table>

Hsiung et al. Movement Disord. 2002: 17:1288
## LONG TERM BENEFITS

<table>
<thead>
<tr>
<th>Disorder</th>
<th>No. of patients with sustained benefits observed at 2 yr (%)</th>
<th>No. of patients with sustained benefits observed at 5 yr (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical dystonia</td>
<td>72/106 (68)</td>
<td>39/62 (63)</td>
</tr>
<tr>
<td>Hemifacial spasm</td>
<td>67/70 (96)</td>
<td>35/40 (88)</td>
</tr>
<tr>
<td>Blepharospasm</td>
<td>33/36 (92)</td>
<td>18/20 (90)</td>
</tr>
<tr>
<td>Focal / segmental</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Writer's cramp</td>
<td>8/14 (57)</td>
<td>5/9 (56)</td>
</tr>
<tr>
<td>Meige's syndrome</td>
<td>4/5 (80)</td>
<td>2/3 (67)</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>2/2 (100)</td>
<td>2/2 (100)</td>
</tr>
<tr>
<td>Jaw opening</td>
<td>0/1 (0)</td>
<td></td>
</tr>
<tr>
<td>Jaw closing</td>
<td>1/1 (100)</td>
<td>1/1 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>187/235 (80)</td>
<td>102/135 (76)</td>
</tr>
</tbody>
</table>

Hsuing et al. Movement Disord. 2002: 17;1288-93
NOVEL THERAPIES

- acetyl hexapeptide 8
- amlodipine
- subdermal delivery of toxin
- liquid abobotulinum A
- TMS
CONCLUSIONS

• Generalized dystonia
  • levodopa trial
  • DBS surgery

• Secondary dystonias
  • combination therapy
  • surgery less effective
CONCLUSIONS

- Focal dystonia
  - botulinum toxin is safe and effective with long term use
  - dose parameters and time between injections need to be respected
  - in short term studies, there are no significant differences in efficacy or side effect profile among different types of botulinum A (Botox, Xeomin, Dysport) and B (Myobloc)
THANK YOU