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. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation. Some forms of dystonia, such as blepharospasm and laryngeal dystonia, are not associated with postures, but are characterized by focal involuntary contractions that interfere with physiological opening or closing of the eyelids or the larynx.

Dystonia is classified along two axes:
1. Clinical characteristics, including age at onset, body distribution, temporal pattern and associated features (additional movement disorders or neurological features)
2. Etiology, which includes nervous system pathology and inheritance.

Phenomenology and classification of dystonia: A consensus update

• 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.
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• Dystonia is classified along two axes:
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  2. Etiology, which includes nervous system pathology and inheritance.

Update on Dystonia, Chorea, and Tics
Joseph Jankovic, MD
Professor of Neurology, Distinguished Chair in Movement Disorders, Department of Neurology, Baylor College of Medicine, Houston, Texas

The prevalence of primary dystonia: A systematic review and meta-analysis
Seives et al. Mov Disord 2012;27:1789-96

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  1. Clinical characteristics, including age at onset, body distribution, temporal pattern and associated features (additional movement disorders or neurological features)
  2. Etiology, which includes nervous system pathology and inheritance.
**Paroxysmal Dyskinesias**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Genotype</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKD</td>
<td>16p11.2-q12.1 (IC)</td>
<td>Proline-rich transmembrane protein 2 gene (PRRT2)</td>
</tr>
<tr>
<td>PNKD</td>
<td>2q33-33 (PNKD)</td>
<td>Paroxysmal kinesigenic dystonia (PRRT2)</td>
</tr>
<tr>
<td>PED</td>
<td>16p12-q12 (ICCA)</td>
<td>Paroxysmal kinesigenic dystonia (PRRT2)</td>
</tr>
</tbody>
</table>

Anticonvulsants: Clonazepam, Anticonvulsants, levetiracetam, BoNT

**The genetics of dystonia: new twists in an old tale.**


- In the past few years, with the advent of new sequencing technologies, there has been a step change in the pace of discovery in the field of dystonia genetics.
- In just over a year, four new genes have been shown to cause primary dystonia (CIZ1, ANO3, TUBB4A and GNAL).
- PRRT2 has been identified as the cause of paroxysmal kinesigenic dystonia.
- Other genes, such as SLC30A10 and ATP1A3, have been linked to more complicated forms of dystonia or new phenotypes.

**A workable strategy for identifying the likely genetic basis for some of the major forms of dystonia**


**Distinguishing features in different types of NBIA.**

- aCP = aceruloplasminemia
- BPAN = beta-propeller protein-associated neurodegeneration
- FAHN = fatty acid hydroxylase-associated neurodegeneration
- INAD = infantile neuroaxonal dystrophy
- KRD = Kufor-Rakeb disease
- MPAN = mitochondrial membrane protein-associated neurodegeneration
- PKAN = pantothenate kinase associated neurodegeneration
- WSS = Woodhouse-Sakati syndrome

**Genetics and Pathophysiology of Neurodegeneration with Brain Iron Accumulation (NBIA)**


<table>
<thead>
<tr>
<th>Condition (Acronym)</th>
<th>Synonym</th>
<th>Gene</th>
<th>Chromosomal position</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKAN</td>
<td>NBIA1</td>
<td>PANK2</td>
<td>20p13</td>
</tr>
<tr>
<td>PLAN</td>
<td>NBIA2, PARK14</td>
<td>PLAX2G</td>
<td>22q12</td>
</tr>
<tr>
<td>FAHN</td>
<td>SPG35</td>
<td>FA2H</td>
<td>16q23</td>
</tr>
<tr>
<td>MPAN</td>
<td></td>
<td>C19orf112</td>
<td>19q12</td>
</tr>
<tr>
<td>Kufor-Rakeb disease</td>
<td>PARK9</td>
<td>ATP13A2</td>
<td>1p36</td>
</tr>
<tr>
<td>Aculeruloplasminemia</td>
<td></td>
<td>CP</td>
<td>3q23</td>
</tr>
<tr>
<td>Neuroferritinopathy</td>
<td></td>
<td>FTL</td>
<td>19q13</td>
</tr>
<tr>
<td>BPAN (SENDA)</td>
<td></td>
<td>n.k.</td>
<td>n.k.</td>
</tr>
<tr>
<td>Idiopathic late-onset cases</td>
<td></td>
<td>Probably heterogeneous</td>
<td>Probably heterogeneous</td>
</tr>
</tbody>
</table>

**T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation.**

McNeill et al. Neurology 2008;70:1614-9

**T2* MRI Scan**

- PKAN 17 y/o
- Infante Neuroaxonal Dystrophy 9 y/o
- Neuroferritinopathy 69 y/o
- Acerulo-plasminemia 55 y/o

**Iron Accumulation**

T2* and FSE MRI distinguishes four subtypes of neurodegeneration with brain iron accumulation.

PKAN 17 y/o
Infantile Neuroaxonal Dystrophy 9 y/o
Neuroferritinopathy 69 y/o
Acerulo-plasminemia 55 y/o

Fast Spin Echo (FSE)

Dystonia

Oral Medications
Levodopa
Anticholinergics
Botulinum Toxin A
Botulinum Toxin B
Surgical Therapies
Chemodenervation
Peripheral Surgeries
Central Surgeries
Selective Peripheral Denervation
Myectomy
Deep Brain Stimulation (Globus Pallidus)

Other Modalities
Constraint Induced Therapy, rTMS

Movement Disorders
Behavioral Symptoms
Cognitive Decline

Huntington Disease

First Symptoms of Huntington Disease

<table>
<thead>
<tr>
<th>Symptom</th>
<th>% of observed</th>
<th># of Pts. *</th>
<th>symptoms **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chorea</td>
<td>877</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Trouble walking</td>
<td>262</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Unsteadiness/imbalance</td>
<td>260</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Difficult to get along</td>
<td>167</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>165</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Clumsiness</td>
<td>154</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Speech difficulty</td>
<td>149</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Memory loss</td>
<td>93</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Trouble holding an object</td>
<td>62</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Lack of motivation</td>
<td>53</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Suspicions/paranoia</td>
<td>48</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Intellectual decline</td>
<td>44</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Changes in sleep</td>
<td>30</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>23</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>20</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Sexual problems</td>
<td>7</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Other mental</td>
<td>363</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Other physical</td>
<td>297</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

*Number of patients from a total of 1,901 with initial symptom information.

**Percent of all observed symptoms from a total of 3,086. Patients could report up to three initial symptoms.

Foroud et al. JNNP 1999;66:52-56


Progression of Huntington Disease

Jankovic J. Lancet Neurol 2009;8:844-56

McNeill et al. Neurology 2008;70:1614-9
Pathology of Huntington Disease

- <40% loss of neurons in SN
- Neuronal intranuclear inclusions formed by aggregation of the N-terminal huntingtin fragments

Huntingtin Gene

Htt (IT15) – 4p16.3

- Encodes a 348 kD, 3144 AA protein, “huntingtin”. Htt
- In HD the polyglutamine segment near the NH$_2$ is elongated

Huntington Disease

<table>
<thead>
<tr>
<th>Age at onset</th>
<th>Juvenile onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>&gt; ~70 - juvenile onset HD</td>
</tr>
<tr>
<td>15 – 55</td>
<td>36-39 CAG repeats - “reduced penetrance”</td>
</tr>
<tr>
<td>5 – 15 years</td>
<td>36-39 CAG repeats - “intermediate”</td>
</tr>
<tr>
<td>~210 Kb</td>
<td>≤ 26 CAG repeats – “normal allele”</td>
</tr>
<tr>
<td>5 – 15 years</td>
<td>≤ 26 CAG repeats – “normal allele”</td>
</tr>
<tr>
<td>&gt;50</td>
<td>CAG Repeats</td>
</tr>
</tbody>
</table>

Atrophy: Putamen > Caudate

HD and Normal

Harris et al. Ann Neurol 1992;31:69-75
Genetic Diagnostic Testing

Autopsy-Proven Huntington Disease with 29 Trinucleotide Repeats

- 65 y/o man with a 5-year history of cognitive decline, chorea, inability to sustain tongue protrusion, gait and balance problems, MMSE 27/30
- 29/20 CAG repeats
- Additional studies were normal including CK, anti-cardiolipin Ab, ESR, thyroid function, blood smear for acanthocytes, and DNA analysis for dentatorubral-pallido-luysian atrophy
- Patient died after a fall during which he suffered SAH
- Autopsy: acute SAH in the right Sylvian fissure; thinning of the cortical ribbon, moderate gliosis and neuronal loss in the caudate and putamen, ubiquitin-positive neuronal intranuclear inclusions in the cortical and other areas
- Patient’s father, who died at age 79, had cognitive decline and involuntary movements. No other FHx of neurologic disorders
- The patient’s “asymptomatic”, 38 y/o, son has 32/19 CAG repeats

Characterization of the Huntington intermediate CAG repeat expansion phenotype in PHAROS.

- The Prospective Huntington At Risk Observational Study (PHAROS) enrolled adults at risk for HD, assessed every 9 months with the UHDRS by investigators unaware of participants’ gene status
- 50 (5.1%) of the 983 participants had an intermediate allele (IA) (27-35 CAG repeats)
- The IA subjects were significantly worse on apathy and suicidal ideation and on 5 of the 9 other behavioral items and on total behavior scores than controls and expanded participants.
- CONCLUSIONS: In a cohort at risk for HD, the IA was associated with significant behavioral abnormalities but normal motor and cognition. This behavioral phenotype may represent a prodromal stage of HD, with the potential for subsequent clinical manifestations, or be part of a distinct phenotype conferred by pathology independent of the CAG expansion length.

A Randomized, Double-Blind, Placebo-Controlled Trial of Tetrabenazine as Antichorea Therapy in Huntington’s Disease (TETRA-HD)

- N = 84 HD subjects randomized, 16 centers
- Tetrabenazine (n = 54) or placebo (n = 30)
- Dosage increased over 7 weeks up to 8 tablets (100 mg) daily, until the desired antichoreic effect or intolerable side effects occurred
- During the last 5 weeks of the study, the dosage remained constant (unless reduced because of intolerable adverse effects)
- Primary outcome: change from baseline in UHDRS chorea score
- Secondary outcomes: CGI, the UHDRS total motor score, functional scales, gait score, tolerability, and safety

Huntington Study Group. Mov Disord 2006;11:136-142

Mean Change in UHDRS Total Maximal Chorea Score (Primary Study Endpoint: From Baseline to Week 12) TETRA-HD

- Mean score decline (UHDRS units): 5.0 (TBZ) vs 1.5 (placebo) (p < 0.0001)

Huntington Study Group. Mov Disord 2006;11:136-142
Tetrabenazine (TBZ) is a centrally-acting, dopamine depleting drug that has been used for treatment of hyperkinetic movement disorders but was not commercially available in the United States until 2008, when the Food and Drug Administration (FDA) approved TBZ for the management of chorea associated with Huntington's disease (HD) under an orphan drug designation.

While sedation, insomnia, mood changes, parkinsonism, and restlessness may occur, these adverse effects can be managed effectively with appropriate titration and monitoring. A black box warning against depression and suicidality warrants careful patient selection, close monitoring and judicious use of antidepressants.

TBZ possesses a unique mechanism of action as a presynaptic dopamine depletor that offers possible advantages over dopamine receptor blocking drugs.

TBZ has a strong potential for application in other hyperkinetic movement disorders, particularly tardive dyskinesia and Tourette syndrome, but randomized, controlled clinical trials are lacking.

Phenocopies of HD

- HDL1 – AD, seizures (prion protein, PRNP; 20p12)
- HDL2 – AD, no seizures (junction protein, JPH3; 16q24.3)
- HDL3 – AR (4p16.3)
- DRPLA – AD (c-Jun NHterminal kinase, JNK; 12p)
- Neuroacanthocytosis – AR (VPS13A, 9q21)
- McLeod syndrome – X-linked (HK, Xp21)
- Mitochondrial encephalomyopathies
- Benign hereditary chorea (NXN2-1/TITF-1, 14q13.1-q21.1)
- Ataxia-Chorea:
  - SCA1 (ataxin-1, CAG expansion, 6p23)
  - SCA2 (ataxin-2, CAG expansion, 12q24.1)
  - SCA17 (TATA-Box binding protein, CAG expansion, 6q27)
  - Friedreich's ataxia (frataxin, GAA expansion, 9p13)
  - Ataxia telangiectasia (protein kinase PI-3, ATM gene, 11q22)
- Neurodegeneration with brain iron accumulation (NBIA)
- Psychogenic chorea
ADHD

TS PLUS

OCD

Tics

Behavioral problems
poor impulse control, self-injurious behavior, and other behavioral problems


Tic Characteristics

- Simple or complex movements (motor) or sounds (phonic)
- Jerk-like (clonic), dystonic, tonic, or blocking
- Premonitory feelings or sensations
- Intermittent
- Repetitive (stereotypic)
- Temporary suppressibility
- Suggestibility
- Increase with stress
- Increase during relaxation after stress
- Decrease with distraction and with concentration
- Waxing and waning, transient remissions
- Persist during sleep

Malignant Tourette Syndrome

- Malignant TS defined as ≥ 2 emergency room visits or ≥ 1 hospitalizations for TS symptoms or its associated behavioral co-morbidities
- Of 332 TS patients evaluated during the three-year period, 17 (5.1%) met criteria for malignant TS
- Compared to patients with non-malignant TS, those with malignant TS were significantly more likely to have a personal history of obsessive compulsive behavior/disorder, complex phonic tics, coprolalia, copropraxia, self-injurious behavior, mood disorder, suicidal ideation, and poor response to medications

In one patient with a “whiplash” tic causing compressive cervical myelopathy, we were able to reverse the neurological deficit with botulinum toxin injections into the cervical muscles. This treatment modality can be particularly effective and even life-saving in patients with tics manifested by severe, repetitive, neck extension. Such tics, if left untreated could result in secondary compressive myelopathy and quadraparesis.


Age When Tic and OCD Symptoms Are at Their Worst

46 children with TS
Structured interview at a mean age of 11.4 years and again at 19.0 years

Tic and OCD Severity at Initial Assessment in Childhood (time 1) and Follow-up in Early Adulthood (time 2)

Tic Severity (N = 46) measured by the Yale Global Tic Severity Scale (YG TSS), OCD (N = 19) by the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

We reviewed medical records of all new TS patients, ≥ 19 y/o on initial evaluation, referred to our Movement Disorders Clinic over the past 5 years, and compared them with 100 TS patients ≤ 18 y/o.

The mean age of 43 adult TS patients was 58.8 ± 6.7 years; the mean age at initial visit of children with TS was 12.9 ± 2.0 years.

Of the adult TS patients, 35 (81.4%) had a history of tics with onset before age 18 (mean age at onset 8.5 ± 3.4 years); 8 (18.6%) reported first occurrence of tics after age 18 (mean age at onset 37.8 ± 13.2 years); only 2 (4.7%) patients reported tic onset after age 50.

Conclusion: Adult TS largely represents re-emergence or exacerbation of childhood-onset TS. During the course of TS, phonic and complex motor tics, self-injurious behaviors, and ADHD tend to improve, but facial, neck and trunk tics dominate the adult TS phenotype.

The bereitschaftspotential in jerky movement disorders.
van der Salm et al. J Neurol Neurosurg Psychiatry 2012;83:1162-7

Deep Brain Stimulation for TS – Target Selection

Bilateral Gpi DBS in TS
Baylor College of Medicine

Deep Brain Stimulation for TS
Baylor College of Medicine

TOURETTE SYNDROME
Therapeutic Strategies

TICS

First Line
Guanfacine
Tetrabenazine

Second Line
Fluphenazine, Risperidone
Atypical Antipsychotics
Clonazepam
Topiramate
BotulinumToxin
Habit Reversal

Third Line
Deep Brain Stimulation

OCD

First Line
Cognitive Behavioral Therapy
SSRI’s

Second Line
Atypical Antipsychotics

ADHD

First Line
Behavioral Therapy
Guanfacine

Second Line
Clonidine
Methylphenidate
Other CNS stimulants
Atomoxetine

Third Line
Deep Brain Stimulation

Decreased binding of [11C]flumazenil: bilateral ventral striatum (VS), bilateral thalamus (Th), right insula (Ins) and bilateral amygdala (Amg)

Increased binding of [11C]flumazenil: bilateral SN, left periaqueductal grey (PAG), right posterior cingulate cortex (PCC) (Cing) and bilateral cerebellum, dentate nuclei (CB).
THANKS