Chorea, Ballism, Athetosis

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Chorea

Chorea (L.; Gr. choreia = dance) is a hyperkinetic movement disorder, characterized by involuntary continuous, abrupt, rapid, brief, unsustained, jerky, irregular movements that flow randomly from one body part to another.

Chorea worsens with stress and may affect fine and gross motor function, activities of daily living, gait and balance, eventually impacting on the quality of life, resulting in markedly increased morbidity and mortality.
Chorea: Associated Features

- Parakinesia (semipurposeful camouflage)
- Motor impersistence ("darting tongue", "milkmaid’s grip")
- “Hung-up” and “pendular” reflexes
- Irregular ("dance-like") gait

Huntington Disease
Differential Diagnosis of Chorea

### Inherited Choreas
- HD (HTT)
- HDL1 (PRNP), HDL2 (JPH3), HDL3
- DRPLA (JNK)
- Neuroacanthocytosis (VPS13A)
- McLeod (HK)
- Brain-Lung-Thyroid (NKK2-1)
- ADCY5-Related movement disorder
- C9orf72 expansion
- NBIA: PKAN, neuroferritinopathy, aceruloplasminemia, infantile neuroaxonal dystrophy (PLA2G6); mitochondrial membrane protein-associated neurodegeneration (MPAN; C19orf12)
- Wilson disease
- Ataxia-chorea: SCA 1,2,3,8,17; Friedreich’s ataxia, AOA, AT
- Mitochondrial disorders
- Other genetic choreas: GNAO1, FOXG1, PDE10A, PDE2A, OPA3, PCCA/PCCB

### Sporadic/Secondary Choreas
- Static encephalopathy - CP
- Sydenham chorea
- Other autoimmune choreas (SLE, APS, NMDAR encephalitis, paraneoplastic syndromes, etc)
- Vascular chorea, polycythemia (JAK2V617F mutation)
- Sporadic C-J disease
- Hyperthyroidism
- AIDS
- Tardive dyskinesia
- Metabolic encephalopathy
  - Hepatolenticular degeneration
  - Non-ketotic hyperglycemia
  - Hypoglycemia
  - Renal failure
  - Ketogenic diet
- Functional (psychogenic) chorea

### Phenocopies of HD

- HDL1 – seizures, psychiatric features
  - AD, prion protein, PRNP; 20p12
- HDL2 – no seizures, blacks of South African origin
  - AD, junctionphilin, JPH3; 16q24.3
- HDL3 (?) – onset 3-4 years, intellectual deficit, dysarthria, dystonia, spasticity, ataxia, Saudi Arabia (1 family)
  - AR, 4p16.3 (?)
- HDL4 (?) = SCA17, markedly heterogeneous presentation
  - AD, TATA-Box binding protein (TBP), CAA/CAG, 6q27
HDL2

- Onset in the 3rd or 4th decade
- Death in 15-25 years
- African (South African founder effect) >>> Hispanic
- Early behavioral changes (social interactions)
- Progressive dementia
- Chorea
- Dystonia
- Parkinsonism
- Weight loss
- Acanthocytosis (?)
- CTG/CAG trinucleotide repeat expansion within the *junctophilin-3 (JPH3)* gene on chromosome 16q24.3 (NL repeat length: 6-27 CTG/CAG triplets, HDL2: 41-58)

HDL2: 56 y/o initially diagnosed with HD, had 22 year hx of progressive changes in memory and personality, involuntary movements, and pseudobulbar affect.
Autopsy: severe striatal atrophy with neuronal loss and gliosis, intranuclear inclusions in the cortex, SN, and thalamus

Walker RH, Jankovic J, O’Hearn E, Margolis RL. Mov Disord 2003;18:1527-30
HDL2
Marked Atrophy of Cerebral Cortex and Striatum

Walker RH, Jankovic J, O’Hearn E, Margolis RL. Mov Disord 2003;18:1527-30

Dentatorubral-Pallidoluysian Atrophy (DRPLA)

• Particularly prevalent in Japan, also UK, US (Haw River syndrome)

• Age at onset: 30 (1st – 7th decade)

• Neuropathology: dentate, red and STN nuclei, GPe > striatum, SN, inf. olive, Purkinje cells, thalamus, lat. corticospinal tract, widespread demyelination and deposition of lipofuscin

• Mutation: Unstable CAG expansion (>35) in the ATN1 gene on chromosome 12p13.31 coding for c-Jun NH(2)-terminal kinase
Dentatorubral-Pallidoluysian Atrophy (DRPLA)

<table>
<thead>
<tr>
<th>Early Onset</th>
<th>Late Onset</th>
</tr>
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<tbody>
<tr>
<td>&lt; 20</td>
<td>&gt; 20</td>
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<tr>
<td>Mild-moderate</td>
<td>Moderate-severe</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Ataxia (severe)</td>
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<tr>
<td>Epilepsy</td>
<td>Choreoathetosis</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>Dystonia</td>
</tr>
<tr>
<td></td>
<td>Rest and postural tremor</td>
</tr>
<tr>
<td></td>
<td>Parkinsonism</td>
</tr>
<tr>
<td></td>
<td>Dementia</td>
</tr>
<tr>
<td></td>
<td>MRI - white matter changes</td>
</tr>
</tbody>
</table>

62 – 79 CAG repeats    54 – 67 CAG repeats

**DRPLA**

41 y/o presented at age 28 with writer’s cramp; later developed chorea, anxiety, and dementia. Her mother and younger brother died of the same disease and another brother was in a NH with the diagnosis of “Huntington disease”.

![Image of person with DRPLA symptoms]
DRPLA
62 y/o woman with severe cerebral white matter changes


Neuroacanthocytosis

“Neuroacanthocytosis”, coined in 1985 to replace Levine-Critchley syndrome and choreoacanthocytosis and to draw attention to the heterogenous presentation with a variety of hyperkinetic and hypokinetic movement disorders in addition to other neurological deficits and abnormal laboratory findings

Familial tic disorder, parkinsonism, motor neuron disease, and acanthocytosis: A new syndrome

We report two brothers who were of consanguineous parents and who displayed a unique association of motor and vocal tics, parkinsonism, distal muscular atrophy and acanthocytosis. In the older brother, leg weakness and muscle wasting started at age 13, and he became wheelchair bound at 40. Electrophysiologic studies and muscle biopsy confirmed diffuse denervation. Involuntary vocalizations and facial tics began at age 36, but within 5 years the tics were replaced by progressive parkinsonism with supranuclear ophthalmoparesis. CSF studies implied impaired central dopamine and serotonin turnover. In the younger brother, orofacial tics started at age 36, vocalizations and fasciculations in the legs began 1 year later, and parkinsonian findings were present at age 40. This is the first report of an association of Tourettism, parkinsonism, motor neuron disease and acanthocytosis occurring as an autosomal recessive syndrome. Suggested the term neuroacanthocystosis.
Neuroacanthocytosis

- Onset: 20-40 yrs
- Autosomal recessive
- Chorea, dystonia, tics, parkinsonism
- Oro-buccal lingual dyskinesias (eating dystonia)
- Behavioral changes, dementia, OCD
- Seizures
- Peripheral neuropathy and myopathy
- Self-mutilation (lip-tongue biting)
- Absent tendon reflexes
- Elevated creatine kinase, liver function tests
- Hepatosplenomegaly

![Image of a mouth showing evidence of neuroacanthocytosis](image-url)
Neuroacanthocytosis

Pathology and Neurochemistry

- Neuronal loss and gliosis in striatum, GP, and SNr

- Autopsy finding in brains of two brothers with neuroacanthocytosis manifested by parkinsonism without chorea showed no significant neuronal loss within the SNc, but there was a low count of parvalbumin positive interneurons in the cortex and striatum

- Axonal neuropathy of large myelinated fibers

- ↓ Substance P in striatum and SN
  ↑ NE in putamen and GP
Neuroacanthocytosis

Laboratory Findings

- Acanthocytosis and echinocytosis; increased yield with dilution in saline, in vitro aging, contact with glass, and scanning EM
- ↑ palmitic acid and ↓ stearic acid in RBCs
- ↑ CK
- EMG/NCV consistent with distal axonal sensorimotor polyneuropathy with dying-back
- PET
  - ↓ Caudate metabolism and striatal CBF
  - ↓ $^{18}$F Dopa uptake in post. put.
  - ↓ $^{11}$F raclopride in caud. > put.

Neuroacanthocytosis

- Autosomal recessive (CHOR-VPS13A, OMIM 605978)
- VPS13A gene (9q21, 73 exons); ~100 different mutations
- Encodes a large protein, chorein (3,174 AAs)
- Chorein required for trafficking of proteins between cell organelles; interferes with membrane functions
- It is widely expressed in various tissues, but its expression is absent or severely reduced in neuroacanthocytosis
- Absence of expression of chorein (Western blot) in RBC membrane is strongly suggestive of a diagnosis of neuroacanthocytosis (www.naadvocacy.org)

Walker et al. Mov Disord 2006;21:1794-805

Neuroacanthocytosis
Absence of Chorein (Western Blot)

Performe by Dr Benedikt Bader, Munich
Neuroacanthocytosis Syndromes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chorea-Acanthocytosis</th>
<th>McLeod Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>VP51.1A</td>
<td>X</td>
</tr>
<tr>
<td>Protein</td>
<td>Chorein</td>
<td>X</td>
</tr>
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<td>Inheritance</td>
<td>Autosomal recessive</td>
<td>X-linked</td>
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<tr>
<td>Acanthocytes</td>
<td><strong>three</strong></td>
<td><strong>three</strong></td>
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<tr>
<td>Cellular compartment</td>
<td>Cytoplasm</td>
<td>Membrane</td>
</tr>
<tr>
<td>Membrane proteins affected</td>
<td>Band3/udacin, actin</td>
<td>Band3/A1R complex, actin-junctional complex</td>
</tr>
<tr>
<td>Red blood cell phenotype</td>
<td>Unaffected</td>
<td>Weak Kell antigens, Rh antigen absent</td>
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<tr>
<td>Serum creatinine kinase level, μL</td>
<td>300-3000</td>
<td>300-3000</td>
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<td>Neuroimaging</td>
<td>Striatal atrophy</td>
<td>Striatal atrophy</td>
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<td>Age of onset, y</td>
<td>20-30</td>
<td>25-60</td>
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<td>Chorea</td>
<td><strong>three</strong></td>
<td><strong>three</strong></td>
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<tr>
<td>Other movement disorders</td>
<td>Feeding and gait</td>
<td>Vocalizations, parkinsonism</td>
</tr>
<tr>
<td></td>
<td>dystonia, tongue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>and lip biting,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>parkinsonism</td>
<td></td>
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<tr>
<td>Seizures</td>
<td>Generalized, partial-complex</td>
<td>Generalized</td>
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<td>Neuromuscular manifestations</td>
<td>Areflexia, weakness, atrophy</td>
<td>Areflexia, weakness, atrophy</td>
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<tr>
<td>Cardiac manifestations</td>
<td>None</td>
<td>Atrial fibrillation, malignant arrhythmias, dilatative cardiomyopathy</td>
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</tbody>
</table>

Roulis et al. JAMA Neurol 2018;75:1554-62

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**McLeod syndrome: Five new pedigrees with novel mutations**

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S. Lakhani1, K. Niotisd, D.W. Scharrede, P. Tuitef, A. Stutzg, C.M. Westhoffh, R.H. Walkeri

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**ABSTRACT**

Objective: To present five new McLeod Syndrome (MLS) pedigrees with novel X gene mutations, review the literature of the disorder, and discuss the typical and atypical clinical features noted with these new mutations.

Methods: This is a multi-center retrospective review of five MLS cases with novel gene mutations. Genotypic and phenotypic information has been obtained from each center.

Results: Five novel mutations are reported in this case series. New clinical findings include prolonged asymptomatic elevated creatine kinase (CK) levels, vocal tics, presence of obstructive sleep apnea (OSA), and one patient of Vietnamese ethnicity.

Conclusion: We expand on the clinical and genetic spectrum of MLS demonstrating the clinical variability of MLS.
Brain-Lung-Thyroid (BLT) Syndrome
“Benign Hereditary Chorea”

- Onset in early childhood; progresses until 2nd decade → static or spontaneously improves (may persist > 60)
- No dementia
- MRI usually normal, but may show hypoplastic pallidum, lack of differentiation of medial and lateral components, and bilateral signal hyperintensities on T2-weighted images
- No pathological changes, but may have reduced number of striatal and neocortical interneurons
- Autosomal dominant – due to mutation in the thyroid transcription factor \( NKK2-1 \) gene on chr 14q13.1–q21.1 (formerly \( TITF1 \))
- \( NKK2-1 \) gene mutations should be considered in patients with chorea, intellectual impairment, growth hormone deficiency, pes cavus, kyphosis, duplex kidney, chronic lung disease, and congenital hypothyroidism
- May improve with levodopa or VMAT2 inhibitors


BLT (Brain-Lung-Thyroid) Syndrome

Peall KJ, Kurian MA. Tremor Other Hyperkinet Mov 2015;5:314

http://www.ncbi.nlm.nih.gov/books/NBK185066/
Since its localization to the \textit{NKX2-1} gene in 2002, the phenotype of the disorder historically called “benign hereditary chorea” has been expanding beyond chorea.

The phenomenology of movement disorders and other symptomatology associated with mutations in \textit{NKX2-1} were characterized after a detailed evaluation of consecutive patients evaluated in our clinic over the past 3 years.

We studied 5 patients (3 females), ages 2-31 years, with confirmed pathogenic variants in \textit{NKX2-1}. All patients exhibited chorea, gross motor delay, and gait impairment. Other symptoms included neonatal respiratory failure (n=4), cognitive deficits (n=3), hypothyroidism (n=4), joint laxity (n=2), myoclonus (n=1), hypotonia (n=3) and seizures (n=1). Chorea often proved refractory to medical therapies.

Conclusion: The phenotype associated with pathogenic variants in \textit{NKX2-1} frequently includes disabling and often medically-refractory neurologic and non-neurologic abnormalities.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>\textit{NKX2-1} pathogenic variant</th>
<th>Chorea</th>
<th>Additional neurologic features (Chorea +)</th>
<th>Gait impairment</th>
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<td>Glik A et al.</td>
<td>2008</td>
<td>4</td>
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<td>✓</td>
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<td>2011</td>
<td>10</td>
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<td>✓</td>
<td>✓ (9/10) Dystonia</td>
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<td>Nakamura K et al.</td>
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<td>Gras D et al.</td>
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<td>✓</td>
<td>✓ Dystonia</td>
<td>Several cases</td>
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<td>Fons C et al.</td>
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<td>1</td>
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<td>McMichael G et al.</td>
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<td>Saligari AP et al.</td>
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<td>Veneziano L et al.</td>
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<td>✓</td>
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<tr>
<td>de Gusmao CM et al.</td>
<td>2015</td>
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<tr>
<td>Parnes et al.</td>
<td>2019</td>
<td>5</td>
<td>✓</td>
<td>✓</td>
<td>✓ Dystonia</td>
<td>✓</td>
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</table>
31 y/o with NKX2-1 mutation and chorea. History of respiratory failure after birth and ongoing thyroid dysfunction. Delayed motor milestones. Initially, chorea well controlled with TBZ but worsened after pregnancy with marked deterioration of gait requiring a walker. She subsequently improved with levodopa. Her daughter also had respiratory failure at birth, generalized chorea and ataxia.
ADCY5-Related Movement Disorder

- Autosomal dominant or recessive disorder caused by mutations in the ADCY5 gene (3p21-3q21.9) that codes for adenyl cyclase 5, a striatal-specific enzyme that converts ATP into cAMP
- The original family was described as “familial dyskinesia and facial myokymia”, but subsequent reports have de-emphasized facial myokymia and focused on a combination of initially paroxysmal and progressive dystonia, chorea, myoclonus, spasticity in the legs, and hypotonia (in the neck and trunk)
- Fluctuating course with episodic exacerbations observed upon awakening, triggered by sleep, intercurrent illnesses, excitement, or stress; attacks may resemble medial frontal lobe seizures (EEG – NL)
- Additional features: language delay, “myopathic facial appearance”, heart failure, often misdiagnosed as cerebral palsy or functional
- No effective pharmacologic treatment, but the following may provide some relief: clonazepam, clobazam, tetrabenazine, acetazolamide, and GPi DBS (Dy et al. J Child Neurol 2016;31:1027-35)

CONCLUSION: Mutations in ADCY5 are responsible for a hyperkinetic movement disorder that can be preceded by episodic attacks before the movement disorder becomes persistent and is frequently misdiagnosed as dyskinetic cerebral palsy. A residual degree of neck hypotonia and a myopathy-like facial appearance are frequently observed in patients with ADCY5 mutations.
### ADCY5-related movement disorders

**Carecchio et al. Parkinsonism Relat Disord 2017;41:37-43**

<table>
<thead>
<tr>
<th>Patient #</th>
<th>ADCY5 mutation</th>
<th>Gender</th>
<th>Family history</th>
<th>AAO (MD)</th>
<th>Current age</th>
<th>Additional signs at onset</th>
<th>MD at onset</th>
<th>Current MD</th>
<th>Nocturnal paroxysms</th>
<th>Diurnal paroxysms</th>
<th>Paroxysmal episodes amelioration</th>
<th>Motor delay</th>
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<tbody>
<tr>
<td>Pt 1</td>
<td>c.1252 C&gt;T; p. R418W</td>
<td>F</td>
<td>N</td>
<td>1.5</td>
<td>15</td>
<td>Axial hypotonia</td>
<td>Paroxysmal dystonic episodes</td>
<td>Chorea, dystonia</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Pt 2</td>
<td>c.1253 G&gt;A; p. R418Q</td>
<td>M</td>
<td>N</td>
<td>1</td>
<td>18</td>
<td>Spastic gait</td>
<td>Paroxysmal dystonic episodes</td>
<td>Myoclonus, dystonia</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Pt 3</td>
<td>c.1252 C&gt;G; p. R418G</td>
<td>M</td>
<td>Y</td>
<td>1</td>
<td>3</td>
<td>Axial hypotonia</td>
<td>Chorea, dystonia</td>
<td>Chorea, dystonia</td>
<td>N</td>
<td>N</td>
<td>NA</td>
<td>Y</td>
</tr>
<tr>
<td>Pt 4</td>
<td>c.1252 C&gt;G; p. R418G</td>
<td>M</td>
<td>Y</td>
<td>3</td>
<td>47</td>
<td>UK</td>
<td>Chorea</td>
<td>Chorea, dystonia</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
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<tr>
<td>Pt 5</td>
<td>c.1252 C&gt;T; p. R418W</td>
<td>F</td>
<td>N</td>
<td>3 mo</td>
<td>35</td>
<td>Axial hypotonia</td>
<td>Chorea</td>
<td>Chorea, dystonia</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
<td>Pt 6</td>
<td>c.1252 C&gt;T; p. R418W</td>
<td>M</td>
<td>N</td>
<td>2</td>
<td>5</td>
<td>Axial hypotonia</td>
<td>Paroxysmal dystonic episodes</td>
<td>Chorea, dystonia</td>
<td>N</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
</tbody>
</table>

**Additional Features:** language delay, myopathic facial appearance, exacerbation during sleep (no EEG correlate), variable course (spontaneous improvement), often misdiagnosed as cerebral palsy

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**ADCY5-Related Movement Disorder**

**Generalized chorea, loss of balance, intermittent hypotonia associated with paroxysmal falls**

**JANUARY 2, 1992**
6 y/o girl with prior diagnosis of dyskinetic cerebral palsy, global developmental delay with moderate intellectual disability. WES revealed a mutation in ADCYS gene. MRI brain was normal.

Courtesy M. Parnes, MD

C9orf72 expansions are the most common genetic cause of Huntington disease phenocopies.

Hensman Moss et al. Neurology 2014;82:292-9

- 10/514 HD phenocopy patients had C9orf72 expansion
- Dystonia, chorea, myoclonus, tremor, bradykinesia, rigidity, and spasticity
- Early depression, obsession, anxiety, apathy, psychosis, cognitive impairment (frontotemporal dementia)
- MRI - atrophy
- Mean age at onset: 42.7 years (8-60)
- 70% had FHx, AD
- Most common genetic cause of ALS
Neuroferritinopathy: Expanding the phenotype and geography
Ondo WG, Adam OR, Jankovic J, Chinnery P. Mov Disord 2010;25:2470-2

72 y/o with 22 yr hx of stereotypy, chorea, OMD, BG abnormalities, and c.460dupA FTL mutation.
49 y/o son with adult onset tics, chorea and similar MRI abnormalities

MRI – Flair
72 y/o

MRI – Flair
49 y/o SON
Overview of genes and pathways involved in neurodegeneration with NBIA

Hayflick et al. Handb Clin Neurol 2018;147:293-305

<table>
<thead>
<tr>
<th>NBIA</th>
<th>Inheritance</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBIA/DYT-PANK2</td>
<td>AR</td>
<td>Pantothenate kinase-associated neurodegeneration (PKAN); dystonia, spasticity, parkinsonism, cognitive decline, eye-of-a-tiger sign (NBIA1)</td>
</tr>
<tr>
<td>NBIA/DYT/PARK-PLA2G6</td>
<td>AR</td>
<td>PLA2G6-associated neurodegeneration (PLAN): dystonia, parkinsonism, cognitive decline, pyramidal signs, psychiatric symptoms (adult phenotype), ataxia (childhood), infantile neuroaxonal dystrophy (NBIA2/PARK14)</td>
</tr>
<tr>
<td>NBIA/CHOREA-FTL</td>
<td>AD</td>
<td>Neuroferritinopathy; dystonia, chorea, parkinsonism, oromandibular dyskinesia, dysphagia, cognitive impairment, behavioral symptoms, low serum ferritin (NBIA3)</td>
</tr>
<tr>
<td>NBIA/MPAN C19orf12</td>
<td>AR/AD</td>
<td>Mitochondrial membrane protein associated neurodegeneration (MPAN); dystonia, levodopa-responsive parkinsonism, tremor, gait impairment, optic nerve atrophy, axonal motor neuropathy; Lewy body pathology (NBIA4)</td>
</tr>
<tr>
<td>NBIA/PARK-WDR45</td>
<td>X-Linked</td>
<td>Beta-propeller protein-associated neurodegeneration (BPAN, previously SENDA syndrome); parkinsonism, dystonia, stereotypies, developmental delay, intellectual disability, behavioral symptoms, autism, seizures, spasticity (NBIA5)</td>
</tr>
<tr>
<td>NBIA/DYT/PARK-CP</td>
<td>AR</td>
<td>Aceruloplasminemia; dystonia, chorea, parkinsonism, tremors, ataxia; cognitive decline, behavioral symptoms, diabetes mellitus, retinal degeneration, anemia, liver iron storage</td>
</tr>
<tr>
<td>HSP/NBIA-FA2H</td>
<td>AR</td>
<td>Fatty acid hydroxylase-associated neurodegeneration (FAHN); spasticity, cognitive decline, cerebellar and brainstem atrophy, dysarthria, dysphagia, optic nerve atrophy, seizures (SPG35)</td>
</tr>
</tbody>
</table>
**GNAO1-Related Movement Disorders**

- 46 patients, AD inheritance
- Severe early-onset hyperkinetic syndrome, with prominent chorea, dystonia and orofacial dyskinesia
- Poorly responsive to medical therapy
- Fluctuates, with critical and life-threatening exacerbations, such as status dystonicus
- The presence of chorea appears to be predictive of a higher risk of movement disorder emergency

**Sex**
- Female 27 (58.7%)
- Male 19 (41.3%)

**Movement disorders features**
- Age in months at MD onset† [mean(median)±SD] 24.2±23.3
- Chorea 27 (58.7%)
- Dystonia 30 (65.2%)
- Dyskinesia 29 (63%)
- MD emergencies 21 (45.7%)
- Need for intensive care hospitalization 19 (41.3%)
- Surgical treatment 10 (21.7%)

**Neuroimaging Features**
- Cortical atrophy 21 (45.7%)
- White matter abnormalities 18 (39.1%)
- Basal ganglia abnormalities 3 (6.5%)
- Epileptic features
  - Epilepsy 22 (47.8%)
  - Epileptic encephalopathy 9 (19.6%)
- Age in months at epilepsy onset [mean(median)±SD] 28.9±43.6
- Total seizure control 10 (45.4%)
- Partial seizure control 1 (4.5%)
- Intractable seizures 5 (22.7%)
- No data 6 (27.2%)
- Follow up data
  - Death 4 (8.7%)
  - Age in years at exitus [mean(median)±SD] 4.8±4.8
  - Age in years at last follow up [mean(median)±SD] 6.9±4.8

**GNAO1-Associated chorea**
3 y/o girl with developmental delay, seizures, chorea exacerbated during febrile illness

Courtesy Dr. Parnes
### Differential Diagnosis of Chorea

#### Inherited Choreas
- HD (*HTT*)
- HDL1 (*PRNP*), HDL2 (*JPH3*), HDL3
- DRPLA (*JNK*)
- Neuroacanthocytosis (*VPS13A*)
- McLeod (*HK*)
- Brain-Lung-Thyroid (*NKK2-1*)
- ADCY5-Related movement disorder
- C9orf72 expansion
- NBIA: PKAN, neuroferritinopathy, aceruloplasminemia, infantile neuroaxonal dystrophy (PLA2G6); mitochondrial membrane protein-associated neurodegeneration (MPAN; C19orf12)
- Wilson disease
- Ataxia-chorea: SCA 1,2,3,8,17; Friedreich’s ataxia, AOA, AT
- Mitochondrial disorders
- Other genetic choreas: GNAO1, FOXG1, PDE10A, PDE2A, OPA3, PCCA/PCCB

#### Sporadic/Secondary Chorea
- Static encephalopathy - CP
- Sydenham chorea
- Other autoimmune choreas (SLE, APS, NMDAR encephalitis, paraneoplastic syndromes, etc)
- Vascular chorea, polycythemia (*JAK2V617F* mutation)
- Sporadic C-J disease
- Hyperthyroidism
- AIDS
- Tardive dyskinesia
- Metabolic encephalopathy
  - Hepatolenticular degeneration
  - Non-ketotic hyperglycemia
  - Hypoglycemia
  - Renal failure
  - Ketogenic diet
- Functional (psychogenic) chorea
Sydenham Chorea
Clinical Features

- Typical age at onset: 7-10, <30 years
- 4-8 weeks after pharyngitis caused by group A β-hemolytic streptococcus (GABHS)
- 70% cardiac (mitral valve) involvement, 30% arthritis
- Chorea in 26% of patients with rheumatic fever, in 20% the only finding
- Usually asymmetrical (20% - hemichorea)
- Individual contractions are slightly longer (>100 msec) compared to HD (50-100 msec), but both have reduced corticospinal excitability as demonstrated by TMS studies (possibly compensatory?)
- Often associated with neuropsychiatric symptoms including ADD, obsessive compulsive behaviors (≤70%), personality changes, emotional lability, anxiety, age-regressed behaviors, and anorexia
- Other features: motor impersistence (tongue darting, milkmaid, and pronator sign), hypometric saccades, tics, clumsiness, dysarthria, hypotonia, and weakness (8% have “chorea paralytica”)
- Usually spontaneously resolves in 3-4 months, but may persist in half of the patients during a 3-year follow up (OCD, ADD)
- May recur during pregnancy (“chorea gravidarum”)
  - 15/20 (75%) patients developed chorea gravidarum
  - All patients with chorea gravidarum who were later treated with oral contraceptives developed recurrence of chorea
Sydenham chorea

Sydenham Chorea
Diagnosis

- The combination of antistreptolysin (ASO), positive in only 10-30% of cases, and antideoxyribonuclease B (ADNaseB) antibodies has a high sensitivity and specificity (also antihyaluronidase and antistreptokinase antibodies)
- MRI is usually normal, but may show enlargement of the striatum and globus pallidus
- 18F-fluorodeoxyglucose PET scan – slightly increased metabolism
Sydenham Chorea
Pathogenesis

• Molecular mimicry between GABHS and CNS antigens
• Antibodies from patients with SC bind to neuronal surface and also target neuronal tubulin
• Rats immunized with GABHS developed antibodies against D1 and D2 receptors and clinically showed compulsive–like behaviors (Brimberg et al. Neuropsychopharmacology 2012;37:2076-87) and passively-transferred serum obtained from GABHS-immunized mice caused behavioral disturbances (Yaddanapudi et al. Mol Psychiatry 2010;15:712-26)
• Antibodies targeting lysoganglioside of group A Streptococcus cross react with dopamine D1 and D2 receptors (Cunningham. Microbiol Spectr 2019;7:4)

Sydenham Chorea
Treatment

• A full 10-day course of oral penicillin V therapy or an injection of benzathine penicillin G
• Penicillin prophylaxis is advisable in all patients for at least 10 years after rheumatic fever or carditis
• A double-blind, placebo controlled study of prednisone showed beneficial effects
  Paz et al. Pediatr Neurol 2006;34:264-9
• Symptomatic treatment
  – Tetrabenazine, valproic acid, and carbamazepine until the condition resolves spontaneously
Sydenham Chorea

Prognosis

A Kaplan-Meyer curve of the time for remission of a cohort of 108 patients with Sydenham chorea prospectively followed

- Self-limited condition with remission after a course of 8–9 months, but up to 50% of patients may remain with chorea after a follow-up of 2 years
- Despite regular use of secondary prophylaxis, recurrences are observed in up to 30% of patients (often without association with streptococcus infection or even anti-basal ganglia antibodies)

Cardoso F. JNNP 2017;88:412-7

Differential Diagnosis of Chorea

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- DRPLA (JNK)
- Neuroacanthocytosis (VPS13A)
- McLeod (HK)
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- Metabolic encephalopathy
  - Hepatolenticular degeneration
  - Non-ketotic hyperglycemia
  - Hypoglycemia
  - Renal failure
  - Ketogenic diet
- Functional (psychogenic) chorea
Diagnostic and Therapeutic Approach to Chorea

Mechanism of action of VMAT2 inhibitors

Vesicular membrane transport type 2 (VMAT2) mediates loading of dopamine into synaptic vesicles for release. Breakdown of dopamine is mediated by monoamine oxidase.

VMAT2 inhibitors block transport of dopamine into synaptic vesicles, reducing dopamine release and depleting dopamine levels through its breakdown by monoamine oxidase.


APLS = antiphospholipid antibody syndrome, BLT = brain-lung-thyroid, BoNT = botulinum toxin, CBZ = carbamazepine, DBS = deep brain stimulation, EU = European Union, GP = globus pallidus internus, IVIG = intravenous immunoglobulin, LID = levodopa-induced dyskinesia, PHT = phenytoin, PKD = paroxysmal kinesigenic dyskinesia, PLEX = plasma exchange/plasmapheresis, rTMS = repetitive transcranial magnetic stimulation, SLE = systemic lupus erythematosus, STN = subthalamic nucleus, TBZ = tetrabenazine, UK = United Kingdom, VPA = valproic acid.

Bashir H, Jankovic J. Expert Rev Neurother 2018;18:51-63
# VMAT Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reserpine</th>
<th>Tetrabenazine</th>
<th>Deutetraabenazine</th>
<th>Valbenazine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Irreversibly binds VMAT</td>
<td>Reversibly binds VMAT2</td>
<td>Reversibly binds VMAT2</td>
<td>Reversibly binds VMAT2</td>
</tr>
<tr>
<td>Binds hVMAT1 (PNS) &amp; hVMAT2 (CNS)</td>
<td>Selectively binds hVMAT2 (CNS)</td>
<td>Selectively binds hVMAT2 (CNS)</td>
<td>Selectively binds hVMAT2 (CNS)</td>
<td>Binds intravesicular site</td>
</tr>
<tr>
<td>Binds cytoplasmic site</td>
<td>Binds intravesicular site</td>
<td>Binds intravesicular site</td>
<td>Binds intravesicular site</td>
<td>Binds intravesicular site</td>
</tr>
<tr>
<td>Several days</td>
<td>Short (T1/2 = 5.5 h)</td>
<td>Intermediate (T1/2 = 6.6 h)</td>
<td>Long (T1/2 = 20 h)</td>
<td></td>
</tr>
<tr>
<td><strong>Duration of action</strong></td>
<td>Frequent</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td><strong>Peripheral side effects:</strong> Orthostatic hypotension, stuffy nose, and gastrointestinal side effects, such as nausea, vomiting, and diarrhea.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CNS: central nervous system; PNS: peripheral nervous system; T1/2: half-life.

Jankovic J. Expert Opin Pharmacother 2016;17:2461-70

---

**Table 3. VMAT2 Inhibitors**

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA-Approved Indication(s)</th>
<th>Formulations</th>
<th>Usual Daily Dosage</th>
<th>Cost¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deutetraabenazine – Austedoi (Teva)</td>
<td>Chorea in Huntington’s disease; Tardive dyskinesia</td>
<td>6, 9, 12 mg tablets</td>
<td>Initial: 6 mg once/d⁴ Maintenance: 6-48 mg in 1 or 2 divided doses²⁺⁴</td>
<td>$9042.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 12-48 mg in 2 divided doses³⁴</td>
<td></td>
</tr>
<tr>
<td>Tetrabenazine – generic Xanazine (Lundbeck)</td>
<td>Chorea in Huntington’s disease</td>
<td>12, 15, 25 mg tablets</td>
<td>Initial: 12.5 mg x 7 d then 25 mg in 2 divided doses Maintenance: 25-50 mg in 2 or 3 divided doses⁶</td>
<td>$3845.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maintenance: 12-48 mg in 2 divided doses³⁴</td>
<td>13,745.60</td>
</tr>
<tr>
<td>Valbenazine – Ingerec® (Neurocine Biosciences)</td>
<td>Tardive dyskinesia</td>
<td>40, 80 mg capsules</td>
<td>Initial: 40 mg once/d x 7 d Maintenance: 80 mg once/d</td>
<td>$6225.00</td>
</tr>
</tbody>
</table>

¹ Approximate WAC for 30 days’ treatment with 42 mg/d of deutetraabenazine 50 mg/d of tetrabenazine, or 80 mg/d of valbenazine WAC = wholesaler acquisition cost or manufacturer’s published price to wholesalers, WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. April 5, 2018. Reprinted with permission by First Databank, Inc. All rights reserved. ©2018. www.fdbhealth.com/policies/drug-pricing-policy.

² The initial daily dose can be increased by 6 mg at weekly intervals until adequate control is achieved (maximum of 48 mg/d).

³ Should be taken with food.

⁴ Daily dosages - 17 mg should be given in two divided doses.

⁵ The daily dose can be increased by 12.5 mg/d at weekly intervals. Dosages of 25 mg/d should be given in 2 divided doses, and dosages of 37.5-50 mg/d should be given in 3 divided doses; single doses should not exceed 35 mg.

⁶ Patients requiring doses >50 mg/d should be tested to determine whether they are poor CYP2D6 metabolizers. The maximum daily dose for CYP2D6 poor metabolizers is 50 mg and the maximum single dose is 25 mg. The maximum daily dose in CYP2D6 extensive and intermediate metabolizers is 100 mg and the maximum single dose is 50 mg.

⁷ Only available at select specialty pharmacies.
Ballism

- Flinging, coarse, random, continuous
- May evolve into chorea or dystonia
- Predominantly proximal
- Usually unilateral (hemiballism), but may be bilateral (paraballism)
- More severe hemiballism tends to be associated with a lesion in the subthalamic nucleus
- Often improves spontaneously
- Levodopa-induced dyskinesia
## Hemiballism – Hemichorea

### Hemiballism-hemichorea

(N = 21)


<table>
<thead>
<tr>
<th>Cause</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>12</td>
</tr>
<tr>
<td>CNS toxoplasmosis (AIDS)</td>
<td>2</td>
</tr>
<tr>
<td>CNS lupus</td>
<td>1</td>
</tr>
<tr>
<td>Arteriovenous malformation</td>
<td>1</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral metastasis</td>
<td>1</td>
</tr>
<tr>
<td>Sydenham's chorea</td>
<td>1</td>
</tr>
<tr>
<td>Neonatal anoxia</td>
<td>1</td>
</tr>
<tr>
<td>Midbrain glioma</td>
<td>1</td>
</tr>
</tbody>
</table>

### Other causes

- Trauma
- Abscesses
- Hyperglycemia
- Vitamin D deficiency
- Multiple sclerosis
- BG calcifications
- Tuberous sclerosis
- Sydenham's disease
- Fisher’s syndrome
- Drugs (levodopa, phenytoin, lamotrigine)
- Other lesions in the STN, internal capsule, cortex, etc
# Hemiballism

## Modern case series of hemiballism

<table>
<thead>
<tr>
<th>Series/reference</th>
<th>Patients with CT or MRI</th>
<th>Lesion in STN</th>
<th>Lesion possibly in STN</th>
<th>Lesion outside STN</th>
<th>No lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghika-Schmid et al.</td>
<td>11</td>
<td>1 (9%)</td>
<td>2 (18%)</td>
<td>0 (0%)</td>
<td>2 (19%)</td>
</tr>
<tr>
<td>Dewey and Jankovic</td>
<td>21</td>
<td>4 (19%)</td>
<td>4 (19%)</td>
<td>6 (27%)</td>
<td>7 (33%)</td>
</tr>
<tr>
<td>Itilovic et al.</td>
<td>22</td>
<td>4 (18%)</td>
<td>3 (14%)</td>
<td>8 (36%)</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>Rido et al.</td>
<td>27</td>
<td>4 (15%)</td>
<td>NA</td>
<td>23 (85%)</td>
<td>NA</td>
</tr>
<tr>
<td>Chung</td>
<td>24</td>
<td>7 (29%)</td>
<td>NA</td>
<td>14 (58%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Our hospital</td>
<td>15</td>
<td>2 (13%)</td>
<td>1 (7%)</td>
<td>7 (47%)</td>
<td>5 (33%)</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>22 (18%)</td>
<td>10 (8%)</td>
<td>64 (53%)</td>
<td>24 (20%)</td>
</tr>
</tbody>
</table>

STN = subthalamic nucleus; NA = not applicable. + For example, in upper brachium or thalamus.

### Other sites: caudate, putamen, pallidum, thalamus, cortex, etc


## Network localization of hemichorea-hemiballismus.

Laganiere et al. Neurology 2016;86:2187-95

- 29 cases of lesion-induced hemichorea-hemiballismus
- Using lesion network mapping, the study showed heterogeneity in anatomical location, but at least 90% of these lesions showed network overlap in the posterolateral putamen
- Hemichorea-hemiballismus lesions are functionally connected to the posterolateral putamen
17 y/o with involuntary movement of RUE for 3 years
L STN-Midbrain AVM

Hemiballism In Acute Hyperglycemia Without Ketosis
**Hyperglycemic chorea/ballism**

- N=7, median age 80 years (range, 53-86)
- Chorea/ballism was unilateral in 6/7 cases and half of these unilateral cases had contralateral putamen T1-hyperintensity on brain MRI.
- After glucose correction, the chorea resolved within one week without recurrence in only one case; among the 6 cases with persistent chorea, it was controlled with dopamine blocking/depleting medications.
- Hyperglycemia causes about 1% of acquired chorea, which is usually persistent.
- Chorea developing within 1 month of an episode of hyperglycemia is suggestive.
- Putamen T1 hyperintensity occurs in half and is often misdiagnosed as hemorrhage.
- May be the presenting feature of type 2 diabetes in advanced age.
- Most cases are unilateral and responsive to dopamine blocking or depleting agents.

Ryan et al. Parkinsonism Relat Disord 2018;48:97-100

**Hemiballism: Prognosis and Treatment**

- Prognosis is usually good
- Therapy should preferentially target the etiology
- If the patient is disabled by the persistent hemiballism, drugs such as dopamine depleters may be tried
- Some patients develop contralateral parkinsonism
- GPi or VIM DBS
Athetosis

- Writhing, random, movements (slow chorea)
- Induced by voluntary movement (“overflow”)
- May co-exist with chorea (choreoathetosis) and dystonia
- Differentiate from pseudoathetosis (loss of proprioception)
- Cerebral palsy is the most common cause of childhood-onset athetosis
Dyskinetic Cerebral Palsy

- CP is a developmental, non-progressive disorder manifested by abnormal movements (chorea, athetosis, dystonia), spasticity and/or ataxia, accompanied by disturbances of cognition, behavior, communication, and other neurologic and musculoskeletal problems.
- CP is attributed to damage in the developing fetal or infant brain, such as perinatal hypoxia-ischemia, intracranial hemorrhage or cerebral infarction, neonatal hyperbilirubinemia (kernicterus), and brain maldevelopment.
- Prevalence: 1.7-3.1/1000 live births, higher in developing countries; the most common cause of disability in early childhood.
- Dyskinetic CP is the third most common form of CP (15%), after spastic (hemiplegic > quadriplegic > diplegic) and ataxic CP.
- Dystonia, choreoathetosis – exacerbated by action
- Exclude CP mimickers, e.g. Dopa responsive dystonia (DRD), Sepiapterin reductase deficiency (SRD), Beta-propeller protein-associated neurodegeneration (BPAN); NKX2-1, ADCY5, GNAO1, KANK1, FOXG1-related disorders, Glut1 deficiency, Ataxia telangiectasia, Congenital disorders of glycosylation (CDG), Lesch-Nyhan, HSP, etc.


70% of CP patients have lesions in the BG or thalamus (10% have normal MRI)

T2-weighted MRI images of the transverse plane and coronal plane
bilateral focal hyperintensity in posterior putamen,
mediolateral thalamus, and central region

Cerebral palsy  
(“Static Encephalopathy”)

**58 brains** (Tsusi et al. Neuropathology 1999;19:14-27)

- 1. microgyria-pachgyria (N = 45)
- 2. thinned cerebral mantle (N = 10)
- 3. hydrocephalus (N = 3)

- Early macrophage reaction, cytokine production, coagulation necrosis, coupled with intrinsic vulnerability of the immature oligodendrocyte → periventricular leukomalacia (Kadhim et al. Neurology 2001;56:1278)

- Perinatal events are most important pathogenic determinants, but genetic factors are increasingly recognized (5-10% family history)

- May be delayed and progressive
Delayed-Onset and/or Progressive Movement Disorder After Static Brain Lesions

* $p < 0.001$ difference compared to adult and to childhood populations

Bilirubin Encephalopathy:
Acute (kernicterus) and Chronic (post-kernicterus)

- Blood group incompatibility between the mother and the fetus → hemolysis → unconjugated bilirubin > 20 mg/dL → CNS damage
- Affects 3% of neonates in developing countries (due to inability to measure total serum bilirubin, high prevalence of 6-phosphate dehydrogenase deficiency, Rh isoimmunization, and sepsis)
- Delayed developmental milestones
- Vertical ophthalmoparesis
- Deafness
- Dysplasia of the dental enamel
- May be delayed and progressive
- MRI - bilateral lesions of GP ± STN

Kernicterus
7 y/o from Nigeria, product of second pregnancy, first pregnancy terminated in stillbirth, neonatal jaundice. Partial deafness, dental problems, mild oculomotor dysfunction

Genetic and metabolic testing on children with global developmental delay: report of the Quality Standards Subcommittee of the AAN and the Practice Committee of the Child Neurology Society.
Michelson et al. Neurology 2011;77:1629-35 (Modified/Updated)

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal Microarray (CMA)</td>
<td>7.8-10.6</td>
</tr>
<tr>
<td>Karyotype studies</td>
<td>4-18.6</td>
</tr>
<tr>
<td>StFISH studies</td>
<td>0.5-7.4</td>
</tr>
<tr>
<td>Targeted genetic testing <em>(PTEN, AKT3 - macrocephaly)</em></td>
<td>1-2</td>
</tr>
<tr>
<td>Ion channel genes <em>(SCN1A, SCN2A, SCN8A, KCNQ2, KCNT)</em></td>
<td>17-42 (males)</td>
</tr>
<tr>
<td>Other genes <em>(GNAO1, STXBP1, FOXG1, CDKL5, KMT2B, SERAC1)</em></td>
<td></td>
</tr>
<tr>
<td>X-linked genetic testing <em>(ARX, JARID1C, SLC6A8, FMR1, MeCP2)</em></td>
<td></td>
</tr>
<tr>
<td>Whole-exome and -genome sequencing (WES, WGS)</td>
<td></td>
</tr>
<tr>
<td>Metabolic testing <em>(inborn errors of metabolism – carbohydrate, amino acid, and lipid, global metabolics)</em></td>
<td>0.2-4.6</td>
</tr>
</tbody>
</table>

www.invitae.com
Medical Treatment of Dyskinetic CP

<table>
<thead>
<tr>
<th>Mechanism of action</th>
<th>Dystonia</th>
<th>Chorea</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deuterotabenazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blocks voltage-gated calcium channel blockers</td>
<td>Used</td>
<td></td>
<td>Nausea, orthostatic hypotension, and constipation.</td>
</tr>
<tr>
<td>Anticholinergic (benztropine)</td>
<td>Used</td>
<td></td>
<td>Nausea, orthostatic hypotension, and constipation.</td>
</tr>
<tr>
<td>Dopamine receptor agonist (bromocriptine)</td>
<td>Used</td>
<td></td>
<td>Sedation, confusion, depression, ataxia, and dyskinesia.</td>
</tr>
<tr>
<td>GABA-A receptor antagonist (tizanidine)</td>
<td>Used</td>
<td></td>
<td>Increased muscle spasticity, sedation, disorientation, dizziness, dry mouth, and increased blood pressure.</td>
</tr>
<tr>
<td>Dopamine receptor antagonist (toleridine)</td>
<td>Used</td>
<td></td>
<td>Decreased muscle tone, confusion, disorientation, hallucinations, orthostatic hypotension, and dyskinesia.</td>
</tr>
<tr>
<td>Pre-synaptic α2 receptor agonist (clonidine)</td>
<td>Used</td>
<td></td>
<td>Orthostatic hypotension, bradycardia, sedation, fatigue, and headache.</td>
</tr>
<tr>
<td>Dopamine antagonist (paliperidone)</td>
<td>Antagonist of D1, D2, and D3 dopamine receptors, and the 5-HT, receptor</td>
<td>Used</td>
<td>Hypotension, sedation, QT interval prolongation, and ventricular arrhythmias (including tachycardia, de-hydratation, and syncope). Overdose causes severe extrapyramidal symptoms.</td>
</tr>
<tr>
<td>Ilmoxamom bromide (tetrabenazine)</td>
<td>Inhibits vesicular monoamine transporter 2, resulting in decreased uptake of monoamines into synaptic vesicles and depletion of monoamine storage</td>
<td>Used</td>
<td>Dementia, Parkinsonism, depression, insomnia, anxiety, and anorexia.</td>
</tr>
<tr>
<td>Mesolimbic depolarizers (ramipril)</td>
<td>Blocks voltage-gated sodium channels</td>
<td>Used</td>
<td>Nausea, vomiting, weight gain, gastrointestinal, gastric ulceration, stomach cramps and diarrhoea, hypertension, body aches, and worsening of ataxia.</td>
</tr>
<tr>
<td>Voltage-gated sodium and calcium channel blocker (candesartan)</td>
<td>Used</td>
<td></td>
<td>Decreased muscle tone, confusion, dizziness, and syncope.</td>
</tr>
<tr>
<td>Calcium channel blocker (verapamil)</td>
<td>Blocks voltage-gated calcium channels, reducing neurotransmitter release and acting as a postsynaptic inhibitor</td>
<td>Used</td>
<td>Nausea, decreased urine, headache, dizziness, and orthostatic hypotension.</td>
</tr>
<tr>
<td>Muscle relaxation (benzodiazepines)</td>
<td>Reduces skeletal muscle tone at the muscle fiber level</td>
<td>Used</td>
<td>Nausea, speech and vocal disfluency, confusion, hallucinations, headache, insomnia and exacerbation of or precipitation of seizures, and increased sedation.</td>
</tr>
<tr>
<td>Voltage-gated calcium channel blocker (gabapentin)</td>
<td>Antagonizes binding of neurotransmitters to voltage-gated calcium channel CaV1 receptors and inhibits synthesis of glutamatergic excitatory transmitters</td>
<td>Used</td>
<td>Dizziness, drowsiness, sedation, fever, fatigue, viral infection, ataxia, and dyskinesia.</td>
</tr>
</tbody>
</table>

Bilateral pallidal deep brain stimulation for the treatment of patients with dystonia-choreoathetosis cerebral palsy: a prospective pilot study
Vidailhet et al. Lancet Neurol 2009;8:709-717

- 13 adults with dystonia-choreoathetosis CP who had no cognitive impairment, little spasticity, and only slight abnormalities of the basal ganglia on MRI.
- The mean Burke–Fahn–Marsden dystonia rating scale movement score significantly improved (24.4%).
- Functional disability, pain, and mental health-related quality of life were significantly improved.

**Conclusion:** Bilateral pallidal neurostimulation could be an effective treatment option for patients with dystonia-choreoathetosis CP. However, given the heterogeneity of motor outcomes and the small sample size, results should be interpreted with caution.
Cerebral Palsy

Movement Disorder
Behavioral problems
Epilepsy
Gl, GU, Respiratory problems
Swallowing Drooling
Low bone density
Socio-economic problems
Nutrition
Pain and distress
Intellectual Impairment
Sleep disturbance
Communication

Treatable Inherited Rare Movement Disorders

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

Mov Disord 2018;33:21-35

Vitamins
abetalipoproteinemia
ataxia VIt E deficiency
biotinidase deficiency
cerebral folate deficiency
cofolamin deficiency
COQ10 deficiency
Homocysteinuria
PDH deficiency

Target reduction
CTX
Manganese transporter
Niemann Pick C
Wilson’s disease

Dietary interventions
abetalipoproteinemia
GLUT1
glutaric aciduria
homocysteinuria
MSUD
methylenomalic aciduria
phenylketonuria
proopionic academia
Refsum

Trigger avoidance
alternating hemiplegia
thiamine transporter
gluturic aciduria
MSUD
methylmalonic aciduria
proopionic academia
rapid-onset D-P

Specific drugs
AADC deficiency
DRD
EA-2
MOCS1
PKD
PTPS
Parkinson’s Disease Center and Movement Disorders Clinic

www.jankovic.org
THANKS