THE DIAGNOSIS AND TREATMENT OF MOVEMENT DISORDERS IN CHILDREN

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ABNORMAL MOVEMENTS: What is the cause? What do we do about it?

- **Step One: Recognize the movement phenomenology**
  - Hyper- or Hypokinetic?
  - One type in isolation, or a combination of abnormal movements?

- **Step Two: Clues from distribution and timing**
  - What body parts are involved, and in what order?
  - Age at onset? Speed of progression? Hour of the day?

- **Step Three: Going from your first best guess to a firm diagnosis**
  - Part of a larger problem, or movements in isolation?
  - What dx is most likely? What meds/interventions, and in what order?
9yo girl with progressive gait abnormality
Dystonia

Q1: Primary or Secondary?
- Big implications for prognosis, treatment choice

Q2: Focal or generalized?
- Focal dystonias can be treated with focal treatments (Botox injections)
- Below the age of 27, most dystonias go on to generalize – be aggressive in your treatment, as things are likely to get worse.

Q3: Is this (1) dystonia in isolation? (2) a compound movement disorder? or (3) is dystonia one symptom in a larger encephalopathic process?
## Primary Dystonias

<table>
<thead>
<tr>
<th>Site of Onset</th>
<th>Age at Onset, Pace and Probability of Generalization</th>
<th>Inheritance</th>
<th>Gene(s)</th>
<th>Penetration</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1</td>
<td>[1, 2, 5, 9] 12{15, 18} 30 40 50</td>
<td>Autosomal Dominant</td>
<td>TorsinA</td>
<td>30 - 40%</td>
<td>Rapidly generalizes, abnormal gait is norm, &gt;50% are Ashkenazi</td>
</tr>
<tr>
<td>DYT2</td>
<td>[1, 2, 5, 9] 12{15, 18} 30 40 50</td>
<td>Autosomal Recessive</td>
<td>Hippocalcin, likely multiple others</td>
<td>100%</td>
<td>Slow generalization, stability, relatively mild</td>
</tr>
<tr>
<td>DYT4</td>
<td>[1, 2, 5, 9] 12{15, 18} 30 40 50</td>
<td>Autosomal Dominant</td>
<td>β-tubulin 4</td>
<td>100%</td>
<td>Most have “whispering” dystonia, occasional cervical or leg involvement</td>
</tr>
<tr>
<td>DYT5a</td>
<td>[1, 2, 5, 9] 12{15, 18} 30 40 50</td>
<td>Autosomal Dominant</td>
<td>GTP cyclohydrolase</td>
<td>Low, 2-3x F&gt;M</td>
<td>Normal development, mood d/o, OCD</td>
</tr>
<tr>
<td>TH deficiency (DYT5b)</td>
<td>[1, 2, 5, 9] 12{15, 18} 30 40 50</td>
<td>Autosomal Recessive</td>
<td>Tyrosine Hydroxylase</td>
<td>100%, variable severity</td>
<td>Sx worsen during day, improve with rest, gait disorder common</td>
</tr>
<tr>
<td>DYT6</td>
<td>[1, 2, 5, 9] 12{15, 18} 30 40 50</td>
<td>Autosomal Dominant</td>
<td>THAP1</td>
<td>60%</td>
<td>All ethnicities, often involves speech, Late upper &gt; lower limb involvement</td>
</tr>
<tr>
<td>Myoclonus Dystonia (DYT11)</td>
<td>[1, 2, 5, 9] 12{15, 18} 30 40 50</td>
<td>Autosomal Dominant, maternal imprinting</td>
<td>Epsilon Sarcolglycan in 30-50%</td>
<td>Complete in paternal lineage</td>
<td>Myoclonus in 100%, Dystonia in 50%. Alcohol responsive symptoms, increased incidence of anxiety and OCD</td>
</tr>
<tr>
<td>DYT12</td>
<td>[1, 2, 5, 9] 12{15, 18} 30 40 50</td>
<td>Autosomal Dominant</td>
<td>ATP1A3</td>
<td>Low at any age, builds over lifetime</td>
<td>Evolution over hours to days, De novo mutations as common as familial</td>
</tr>
<tr>
<td>DYT16</td>
<td>[1, 2, 5, 9] 12{15, 18} 30 40 50</td>
<td>Likely Autosomal Recessive</td>
<td>PRKRA</td>
<td>Unknown</td>
<td>50% have parkinsonism, Refractory to therapy</td>
</tr>
</tbody>
</table>

Match your patients:
- Site of Onset
- Age at Onset
- Rate of Progression
- Inheritance

And you will find a short list of genes to test

To read more about the primary dystonias: Waugh and Sharma, “Dystonia: From genotype to phenotype” Neurology Clinics, Nov 2013
If Dystonia is...

- Focal to limited-segmental – Botox injections
  - EMG guidance very important
  - q3mo initially, but can often wean to q4, q5 over time

- Widely-distributed – meds +/- Botox
  - Dopamine replacement: carbidopa/levodopa, start at 1-2 mg/kg/day, increase to 10mg/kg/d for one month
  - Trihexyphenidyl (Artane): start at 1-2mg daily, increase q1-2 weeks by 1mg or 15-20% daily (whichever is smaller)
  - Benzodiazepines: longer-duration better, e.g. clonazepam

- If meds and Botox are insufficient, consider evaluation for deep brain stimulation (DBS)
WHAT IS DBS?

- Three implanted parts:
  - Electrodes in the brain
  - Stimulator (battery and computer) in the torso
  - Connecting wires between the two

- Battery lasts 3-7 years – will require replacement

- Electrodes and connectors remain implanted – we hope to never touch them again
Deep Brain Stimulation
Overview

Stimulator leads

Extensions

Neurostimulator (under skin)
Neurostimulator Implantation Phase

- Stimulator leads connected to
  Extension leads
- Incision behind ear
- Leads attached to neurostimulator
- Incision below collar bone
1 MONTH POST SURGERY

Doctor using wireless programmer to test device

Programmer
9yo girl with gait abnormality, now 3 months post-DBS
8yo boy with abnormal gait
DBS IS HIGHLY EFFECTIVE IN PRIMARY DYSTONIAS.
WHAT ABOUT FOR THE OTHER 90%?

For secondary dystonias, the published rate of improvement is 30-40%. But that’s in all etiologies and ages…
1. Different etiologies certainly have different response rates

2. Improvement on formal dystonia scales may be less important than family-judged areas of benefit
   - Gimeno H et al., Eur J Pedi Neuro 2012

3. For younger children, formal dystonia scales are less accurate and are less able to recognize benefit.
   - Kuiper M et al., Mov Dis Clin Practice 2016
WHEN TO REFER FOR DBS?

- Any confirmed- or presumed-genetic primary dystonia
- Though primary dystonias respond better, consider DBS in secondary dystonias when:
  - Dystonia >> spasticity (in severity or impact)
  - Shorter duration of dystonia +/- younger age
  - Absence of joint contractures
- If DBS is not an option for your 2ndary dystonia patient, spasticity treatments such as intrathecal baclofen pump or selective dorsal rhizotomy may be helpful
A 6 YEAR OLD GIRL WITH HYPERKINETIC MOVEMENTS
2yo girl with hypotonia and motor delay
PRIMARY CHOREA IN THE FIRST 2Y OF LIFE

- ADCY5-related dyskinesias
  - Adenylate cyclase, 5th subunit
  - More severe, more disabling
  - Can be continuous or paroxysmal
  - Unique feature: movements WORSEN in sleep
  - Normal cognition in most; severe chorea ≈ Dev Delay

- Benign hereditary chorea
  - NKX2.1, aka TITF1
  - Chorea is rarely disabling, improves by 3rd decade
  - Myoclonus, dystonia as well
  - Mild learning disabilities, Dev Delay
Striatal Circuits Give Important Clues to Understanding ADCY5 and NKX2.1-related Movement Disorders

To read more, see “Time is On our Side: Age as a Diagnostic and Pathologic Clue in Pediatric Movement Disorders.” Dy, Aravamuthan, and Waugh Scientific American Neuro, Aug. 2016
10 yo boy with onset and worsening of movements over 48 hours
SYDENHAM CHOREA – CHARACTERISTICS

- The most common cause of acute chorea in children
- Symptoms develop over a few hours or days
- Historical note (1969, SK Wilson): The child with SC is thrice cursed: “once for general fidgetiness, once for breaking crockery, and once for making faces at his grandmother”
- Chorea plus… akathisia; diffuse, mild hypotonia; changes in personality; emotional lability; moderate behavioral regression; dysarthria; moderate gait disturbance with few falls
- Largely confined to ages 5y-prepubertal years, F > M
- Strep-related anti-basal ganglia antibodies present
SYDENHAM CHOREA – PROGNOSIS

- Chorea resolves <6mo in ~half, can take 2y. Rarely, permanent.
- Up to 20% of children with SC develop ADHD or OCD-like symptoms
- 2/3 are left with bradykinesia, many have executive function deficits
- One third have recurrence with subsequent strep infection.
CHOREA IN LUPUS

- Uncommon among all lupus sufferers, but...
- When chorea is the first symptom of lupus, it is commonly seen in isolation
- Lupus should be in the differential for all acute-onset choreas, especially in teens or with any signs of systemic inflammation
CHOREA IN NEURODEGENERATIVE DISEASE

- Childhood-onset Wilson disease often presents with both chorea and dystonia
- Juvenile Huntington disease (late teens) rare but important to keep in mind
- Onset of HD in childhood rarely has chorea in first few years. Instead, presents with parkinsonism +/- dystonia – the Westphal variant.
- A huge number of metabolic disorders / brain injuries can cause chorea – see appendix at the end, DDx for chorea is 4p!
TREATMENT OF CHOREA

- ADCY5-related dyskinesias: DBS?
- NKX2.1/BHC: dopamine supplementation, tetrabenazine, propranolol, valproate
- Sydenham: immunosuppression, benzodiazepines, valproate
- Choreoathetoid cerebral palsy, basal ganglia injury from toxins or metals: tetrabenazine, benzodiazepines
- Wilson disease, lupus, NMDA-R encephalitis: treat the underlying condition
2 WEEK OLD BOY WITH JERKING MOVEMENTS
**Benign Neonatal Sleep Myoclonus**

- Typical onset – a few days to a few weeks.
- (usually) Resolves by 6mo, most within 3mo of onset.
- Distal > proximal limbs, more prominent in upper than lower extremities, often bilateral, can be unilateral
- Sometimes accompanied by facial or axillary myoclonus
- Can be rhythmic or non-rhythmic
- Occur in clusters lasting seconds, but may have many clusters over minutes. Rarely, reported to last >30m
- Mostly occurs during quiet sleep – disappear with wakening in most, though 5-10% will continue into sleep-wake transition
- Worsen with benzodiazepines
Benign neonatal sleep myoclonus.
Coulter DL, Allen RJ.

The first published account of BNSM!
BENIGN MYOCLONUS OF INFANCY

- Age at onset: 1–18 months, median of 6 months.
- Combination of the following, half of the time in clusters
  (1) myoclonus (positive or negative)
  (2) spasms and brief tonic contractions
  (3) shuddering
  (4) atonia or negative myoclonus
- Majority occur only while awake
- Fades 6-12 months after onset, 100% benign prognosis
- aka Fejerman syndrome

- adapted from Caraballo RH, Epilepsia 2009
CLASSIFYING MYOCLONUS

1. Epileptic vs. Non-Epileptic
2. Co-incidence with other Movement Disorders
   3. Primary vs. secondary to injury or degeneration
   4. Focal - Segmental - Multifocal - Generalized
3. Spontaneous - Stimulus sensitive/Reflex - Action induced
4. Anatomical origin: Cortical, Subcortical, Spinal cord, Periphery

Why classify?
(1) Certain types of myoclonus indicate specific disorders
(2) Effective treatments are specific to physiology - characterizing the movements often yields better outcomes
(3) By classifying the movements, the clinician gains a greater understanding of the process that yields the movements.
Take home point: for any grade-school to high-school aged child with isolated myoclonus, you must evaluate for epilepsy.
How do you quantify myoclonus?

- While standardized instruments exist (the Unified Myoclonus Rating Scale), they are cumbersome and take too long for routine clinical use.
- Next best thing? A cup.
A Twitchy 20yo Man
MYOCLOONUS-DYSTONIA (DYT11)

- Onset from early childhood to late adolescence
- Myoclonus in all; dystonia in half
- Myoclonus is action-induced and predominantly affects the head, neck and shoulders
- EtOH reduces symptoms for many, not all
- Commonly have comorbid psychiatric disorders
- Dominant with variable penetrance – maternal inheritance is relatively protective (~10% penetrance)
- No Epsilon-sarcoglycan gene mutation? Then called DYT15, recently identified link to KCTD17 gene
ESSENTIAL MYOCLONUS ≈ MYOCLONUS-DYSTONIA

Before Alcohol

After Alcohol
OTHER RELATIVELY-COMMON TYPES OF MYOCLOCUS

- Opsoclonus-Myoclonus-Ataxia (all 3, or any 1 in isolation)
- Myoclonus-Ataxia – often the initial presentation of ataxia telangiectasia
- Post-anoxic myoclonus – both immediate post-injury (hours-day) and later (the Lance-Adams syndrome)
- Myoclonic tics

Key distinction: presence of progressive encephalopathy vs. isolated disorders of movement
TREATMENT

- Therapy only suppresses symptoms, does not remove cause
- Primary drugs used to treat myoclonus:
  - levetiracetam, valproic acid, zonisamide
  - clonazepam, primidone, and acetazolamide.
- Mostly, treatment based on expert opinion – a single RCT demonstrating efficacy for zonisamide in DYT11
- Choice of drugs is based upon questions from 3-step diagnostic approach—the fundamental cause and origin of the movements—and the side-effect profile of the agents.
- DBS – highly effective for myoclonus in DYT11 (>90% reduction), 50-75% benefit for dystonia
The most common movement disorder in adults

In 30-50% of adult ET cases, symptoms begin in childhood – mean: 6-7 years. M > F

Dominantly inherited with variable severity within a family, but penetrance is 100% by the age of 60.

Very slowly progressive (years to decades), exacerbated by stress.

Two peaks of referral: school-age children, late adolescence

In children ET is typically a mixed postural and action tremor which affects the hands much more than the legs, neck, or voice. Tremor is always bilateral, though may be moderately asymmetric.
3 READILY-DISTINGUISHABLE DYSKINESIAS

- Paroxysmal Kinesigenic Dyskineisa - PKD
- Paroxysmal Nonkinesigenic Dyskinesia – PNKD
- Paroxysmal Exertional Dyskinesia – PED

**Timing**

- 100’s per day, but short? PKD
- A few per year, but lasting hours/days? PNKD
- With exercise lasting longer than 10-20min? PED
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- Paroxysmal Exertional Dyskinesia – PED

Phenomenology

- Unilateral or highly asymmetric? PKD, PED (if unilat. exercise)
- Triggers?
  - Movement or plan to move? PKD
  - Foods, alcohol, illness, fatigue, emotional stress? PNKD
  - Exercise or fasting? PED
3 READILY-DISTINGUISHABLE DYSKINESIAS

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- Paroxysmal Nonkinesigenic Dyskinesia – PNKD
- Paroxysmal Exertional Dyskinesia – PED

**Treatment**

- PKD – Carbamazapine 25-50mg qDay. Also effective: oxcarbazepine, lamotrigine, phenytoin, acetazolamide
- PNKD – Avoidance of triggers. Less effective: clonazepam, carbamazapine, levetiracetam. DBS?
- PED – Ketogenic diet
3 READILY-DISTINGUISHABLE DYSKINESIAS

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- Paroxysmal Exertional Dyskinesia – PED

**Genetic Causes**

- PKD – PRRT2 gene in ~50% of all cases, most of familial cases
- PNKD – MR1 gene
- PED – SLC2A1 mutations in most; PDHA1, ECHS1 in one case ea.
INCREASING RECOGNITION OF MIXED MOVEMENT DISORDERS IN CHILDREN
40mo in a busy tertiary pediatric hospital – all inpatient or ER movement disorder consults
- Chorea – 38%
- Dystonia – 33%
- Tremor – 23%
- Myoclonus – 19%
- Parkinsonism – 19%

Most common cause: Inflammatory / Infectious – 42%
23% later proved to be functional/conversion

RC Dale et al., Dev Med Child Neuro. Aug 2010
IN SUMMARY:

- Phenomenology is your most important clue
- Age, location, and rate of progression further refine your list
- Most patients fall into a small list of candidates – but beyond those less-obscure disorders, MANY metabolic and heredo-degenerative syndromes can cause movement disorders.
- In our clinics, following exhaustive diagnostic workup we remain without a genetic diagnosis in ~50%
- When you consider DBS, early treatment – before loss of joint mobility – strongly influences outcome. Refer early!
SEIZURE TYPES WITH MYOCLONUS AS A PROMINENT FEATURE

- 20% of neonatal seizures (all types) are myoclonic (Volpe)
- Severe Myoclonic Epilepsy of Infancy – Dravet syndrome
- Myoclonic-astatic epilepsy of childhood – Doose syndrome
- Juvenile Myoclonic Epilepsy – <5% have only myoclonus, but myoclonus often begins before other recognized seizure types
# AGE-DEPENDENT HEREDODEGENERATIVE DYSTONIAS

## Onset Before Two Years of Life

<table>
<thead>
<tr>
<th>Disorder (including parallel nomenclatures)</th>
<th>Relationship of dystonia to other features</th>
<th>Gene</th>
<th>Inheritance pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutaric academia type I</td>
<td>Dystonia is usually progressive, often onsets after acute encephalopathic crisis</td>
<td>GCDH</td>
<td>Recessive</td>
</tr>
<tr>
<td>Idiopathic basal ganglia calcification, Familial Fahr disease</td>
<td>Coexists with severe developmental delay, epilepsy, hypotonia</td>
<td>Unknown</td>
<td>Recessive</td>
</tr>
<tr>
<td>NBIA2A and -B, PLAN, infantile neuroaxonal dystrophy (INAD)</td>
<td>PLA2G6 mutations cause a wide array of phenotypes: psychomotor regression and ataxia with eye movement abnormalities and optic atrophy (INAD); early global developmental delay and hypotonia, progressing to myoclonic epilepsy, ataxia, chorea, and dystonia (PLAN); adult-onset dystonia-parkinsonism.</td>
<td>PLA2G6</td>
<td>Recessive</td>
</tr>
<tr>
<td>Methylmalonic aciduria</td>
<td>Dystonia is common and may be transient with metabolic crises, persistent after basal ganglia infarction</td>
<td>MUT, several others</td>
<td>Recessive</td>
</tr>
<tr>
<td>Lesch-Nyhan disease</td>
<td>Psychomotor retardation typically precedes dystonia/chorea</td>
<td>HPRT</td>
<td>X-linked</td>
</tr>
<tr>
<td>Hypomyelinating leukodystrophy (HLD1), Pelizaeus-Merzbacher disease</td>
<td>Choreaathetoid movements are more common, dystonia is rare</td>
<td>PLP1</td>
<td>X-linked, rare female symptomatic carriers</td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>Dystonia occurs late and most likely affects the legs</td>
<td>MECP2</td>
<td>X-linked dominant</td>
</tr>
<tr>
<td>Subacute necrotizing encephalomyelopathy, Leigh Syndrome</td>
<td>Dystonia, chorea, and ataxia are common, unlikely to be found in isolation</td>
<td>Many</td>
<td>Mitochondrial or Recessive</td>
</tr>
<tr>
<td>Disorder (including parallel nomenclatures)</td>
<td>Relationship of dystonia to other features</td>
<td>Gene</td>
<td>Inheritance pattern</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>--------------------------------------------</td>
<td>------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Wilson disease</td>
<td>Uncommon finding, late onset of neurological symptoms</td>
<td>ATP7B</td>
<td>Recessive</td>
</tr>
<tr>
<td>Friedreich ataxia</td>
<td>Multiple movement disorders can occur following onset of ataxia: postural tremor is the most common, dystonia common, chorea unusual</td>
<td>FXN</td>
<td>Recessive</td>
</tr>
<tr>
<td>Ataxia telangiectasia</td>
<td>Dystonia and/or chorea develop in ~90%, well after ataxia is evident</td>
<td>ATM</td>
<td>Recessive</td>
</tr>
<tr>
<td>Fucosidosis</td>
<td>Lower extremity dystonia described in a single patient</td>
<td>FUCAI</td>
<td>Recessive</td>
</tr>
<tr>
<td>PKAN, PANK-2 deficiency, Neurodegeneration with brain iron accumulation (NBIA) type I</td>
<td>Gait abnormalities, psychomotor decline, chorea, and dystonia are all reported presenting symptoms. Dystonia is a universal feature, usually generalized with prominent oromandibular dystonia</td>
<td>PANK2</td>
<td>Recessive</td>
</tr>
<tr>
<td>Juvenile G_{452} gangliosidosis, Juvenile Tay-Sachs disease</td>
<td>Dystonia and/or chorea are rare and late findings</td>
<td>HELX1</td>
<td>Recessive</td>
</tr>
<tr>
<td>HDL3, Huntington disease-like 3</td>
<td>Dystonia presents early, often with chorea and ataxia.</td>
<td>4p15.3</td>
<td>Recessive</td>
</tr>
<tr>
<td>Niemann-Pick C, types I and II</td>
<td>Type I: ataxia and myoclonus are common, dystonia rare Type II: chorea, facial dyskinesias common, dystonia rare</td>
<td>NPC1, HE1</td>
<td>Recessive</td>
</tr>
<tr>
<td>Woodhouse-Sakati syndrome</td>
<td>Cognitive impairment often present in childhood, with later development of other syndromic features. Dystonia and/or chorea are quite common.</td>
<td>C2orf57</td>
<td>Recessive</td>
</tr>
<tr>
<td>Dystonia-deafness syndrome, Mohr-Tranebaerg syndrome</td>
<td>Progressive deafness after 2 years of life, later dystonia</td>
<td>TIMM8A/DDP1</td>
<td>X-linked, mild symptoms in some female carriers</td>
</tr>
<tr>
<td>Marsden variant of Leber hereditary optic neuropathy</td>
<td>Dystonia often precedes optic atrophy. Dystonia may be isolated in an individual in which familiar Leber alone or Leber plus dystonia are seen.</td>
<td>MTND1, MTND3, MTND4, MTND6</td>
<td>Mitochondrial</td>
</tr>
</tbody>
</table>
## AGE-DEPENDENT HEREDO-DEGENERATIVE DYSTONIAS

### Onset in Adolescence

<table>
<thead>
<tr>
<th>Disorder (including parallel nomenclatures)</th>
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<th>Gene</th>
<th>Inheritance pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA3, Machado-Joseph disease type 1</td>
<td>Usually follows ataxia, but dystonia may rarely be the presenting feature</td>
<td>ATXN3</td>
<td>Dominant with anticipation. Reduced penetrance in intermediate copy-number carriers</td>
</tr>
<tr>
<td>SCA7</td>
<td>Dystonia and/or chorea may result, though usually years after ataxia presents. Also have retinal degeneration and optic atrophy, bulbary palsies, and dementia. Highly variable between and within families.</td>
<td>ATXN7</td>
<td>Dominant with anticipation. Onset is usually in mid-life, with only occasional onset in late-teens</td>
</tr>
<tr>
<td>SCA17</td>
<td>Focal dystonia is the presenting symptom in rare kindreds. Typically dystonia, chorea follow ataxia, dysphagia, and/or psychiatric symptoms.</td>
<td>TBP</td>
<td>Dominant with anticipation, reduced penetrance in intermediate copy-number carriers</td>
</tr>
<tr>
<td>Huntington Disease</td>
<td>Dystonia is common but not a universal feature. Younger ages are more likely to manifest as the Westphal variant of HD, with hypokinetic rigidity instead of chorea</td>
<td>IT15</td>
<td>Dominant with anticipation, complete penetrance</td>
</tr>
<tr>
<td>Neuroferritinopathy, NBIA3</td>
<td>Present with chorea &gt; focal limb dystonia &gt; parkinsonism. Typical onset is in the 20s-30s, though onset in the teens has been reported.</td>
<td>FTL</td>
<td>Dominant</td>
</tr>
<tr>
<td>PARK9, Kufor-Rakeb syndrome</td>
<td>Parkinsonism is primary, rapidly progressive, frequently develop moderate dystonia and/or myoclonus</td>
<td>ATP13A2</td>
<td>Recessive</td>
</tr>
<tr>
<td>PARK2</td>
<td>Focal dystonias, especially of the feet, follow onset of parkinsonism</td>
<td>PRKN</td>
<td>Recessive</td>
</tr>
<tr>
<td>Chorea acanthocytosis</td>
<td>Chorea is near-universal; dystonia, tics, and parkinsonism are less common. Onset is usually in the 20-40s</td>
<td>VPS13A (Chorion)</td>
<td>Recessive, rare reports of apparent dominant inheritance</td>
</tr>
</tbody>
</table>
Static injury
- Kernicterus
- Hypoxic/ischemic insult (e.g., infarct, cardiac arrest, cardiac bypass, perinatal hypoxia, polycythemia
  vera, moyamoya, bronchopulmonary dysplasia in infants, carbon monoxide inhalation)
- Toxin induced (ethanol, methanol, toluene, bismuth, manganese, thallium, mercury)
- Infections (mycoplasma, Lyme, legionella, toxoplasmosis, HIV, HSV, measles (SSPE), mumps, varicella,
  parvovirus B19)
- Trauma
- Midline CNS malformation disorders (holoprosencephaly, Joubert, agenesis of the corpus callosum)

Autoimmune and inflammatory syndromes
- Sydenham chorea
- Systemic lupus erythematosus
- NMDA-receptor encephalitis
- Behçet disease
- Antiphospholipid antibody syndrome
- Acute disseminated encephalomyelitis
- CNS vasculitis
- Rasmussen encephalitis
- Multiple sclerosis (rare symptom)
- Acute necrotizing encephalopathy (late finding)
Endocrine or nutritional derangement
- Hyper- or hypoglycemia
- Hyper- or hyponatremia
- Hyperthyroidism
- Hypoparathyroidism
- Hypomagnesemia
- Vitamin B12 deficiency in infancy
- Chorea gravidarum

Drug exposure
- Dopamine agonists (amphetamine, cocaine, methylphenidate, pemoline, levodopa)
- Dopamine antagonists (neuroleptics, antiemetics)
- Anticonvulsants (phenytoin, carbamazepine, phenobarbital)
- Calcium channel blockers
- Anticholinergics
- Antihistamines
- Oral contraceptives (reactivation of Sydenham chorea? Often hemichorea)
- Lithium
Differential Diagnosis of Chorea,

Neurodegenerative disorders

- Huntington disease (juvenile onset, unlikely in childhood onset)
- Wilson disease (chorea, dystonia are more common in younger-onset patients)
- Neuroacanthocytosis (unusual for chorea to present before 20 years, also with dystonia and parkinsonism, predilection for orolingual dyskinesias)
- Lesch-Nyhan disease
- Ataxia telangiectasia
- Leigh disease, other mitochondriopathies
- Pantothenate kinase-associated neurodegeneration (PKAN – dystonia and spasticity are typical)
- Spinocerebellar ataxias 1, 2, 3, 6, 17
- Dentatorubropallidoluysian atrophy (DRPLA)
- Fahr syndrome (chorea usually in association with other neuropsych symptoms)
**Metabolic syndromes**
- Pelizaeus-Merzbacher disease type I
- Glutaric acidemia
- Propionic acidemia
- Homocystinuria
- Phenylketonuria
- Costoff syndrome (3-methylglutaconic aciduria)
- Cerebral folate deficiency
- Sulfite oxidase deficiency
- Pyruvate carboxylase deficiency
- Biotinidase deficiency

**Mass lesions**
- Tumor, CNS lymphoma, abscess, arteriovenous malformation, cavernous hemangioma