Clinical spectrum of genetic pediatric movement disorders

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Objectives

- Review basic classification of pediatric hyperkinetic movement disorders.
- Describe the definition and phenomenology of dystonia, chorea and myoclonus.
- Become familiar with genetic pediatric movement disorders through video cases.
Disclosures

- I have no conflict of interest to disclose.
- I receive funding from the American Academy of Neurology Clinical Research Training Fellowship.
Hyperkinetic movement disorders

- Benign
- Acquired
- Genetic
  - Isolated
  - Neurometabolic/Complex
Hyperkinetic movement disorders

- Dystonia
- Chorea
- Athetosis
- Myoclonus
- Ballismus
- Tremor
- Tics
- Stereotypies
Dystonia

- Dystonia is characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
- Dystonic movements are typically patterned, twisting, and may be tremulous.
- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.
Dystonia phenomenology

• Dystonic tremor
  • A spontaneous oscillatory, rhythmical, although often inconstant, patterned movement.
  • Null point when tremor is relieved by allowing the abnormal dystonic posture to fully develop.

• Overflow
  • unintentional muscle contraction of other regions which accompanies primary dystonic movement.

• Mirror dystonia
  • unilateral movement usually in the more severely affected side, when contralateral movements or actions are performed.

• Geste antagoniste (sensory trick)
  • Voluntary actions that specifically correct the abnormal posture or alleviate the dystonic movements.
Dystonia classification

**Axis I. Clinical characteristics**

**Clinical characteristics of dystonia**

- **Age at onset**
  - Infancy (birth to 2 years)
  - Childhood (3–12 years)
  - Adolescence (13–20 years)
  - Early adulthood (21–40 years)
  - Late adulthood (>40 years)

- **Body distribution**
  - Focal
  - Segmental
  - Multifocal
  - Generalized (with or without leg involvement)
  - Hemidystonia

- **Temporal pattern**
  - Disease course
    - Static
    - Progressive
  - Variability
    - Persistent
    - Action-specific
    - Diurnal
    - Paroxysmal

- **Associated features**
  - Isolated dystonia or combined with another movement disorder
    - Isolated dystonia
    - Combined dystonia
  - Occurrence of other neurological or systemic manifestations
    - List of co-occurring neurological manifestations

**Axis II. Etiology**

- **Nervous system pathology**
  - Evidence of degeneration
  - Evidence of structural (often static) lesions
  - No evidence of degeneration or structural lesion

- **Inherited or acquired**
  - Inherited
    - Autosomal dominant
    - Autosomal recessive
    - X-linked recessive
    - Mitochondrial
  - Acquired
    - Perinatal brain injury
    - Infection
    - Drug
    - Toxic
    - Vascular
    - Neoplastic
    - Brain injury
    - Psychogenic

- **Idiopathic**
  - Sporadic
  - Familial

Albanese A et al, Mov Dis, Vol. 28, No. 7, 2013
Dystonia genes

![Diagram of DYT genes]

DYTs: Phenotypes and Genotypes

- Isolated dystonias
  - Persistent
    - Parkinsonism
      - DYT-TOR1A (DYT1)
      - DYT-THAP1 (DYT6)
      - DYT-GNAL (DYT25)
    - Myoclonus
      - DYT-GCH1 (DYT5a)
      - DYT-TH (DYT5b)
      - DYT-ATP1A3 (DYT12)
      - DYT-TAF1 (DYT3)*
    - Mixed
      - DYT-PRRT2 (DYT10)
      - DYT-MR1 (DYT8)
      - DYT-SLC2A1 (DYT18)

- Combined dystonias
  - Persistent
  - Paroxysmal

*Cystic fibrosis transmembrane conductance regulator associated protein 3 (CFTR-Associated Protein 3)
Genetic dystonia in childhood

<table>
<thead>
<tr>
<th>DYT Number</th>
<th>Paroxysmal/Nonparoxysmal</th>
<th>Clinical Presentation</th>
<th>Pattern of Inheritance</th>
<th>Causative Gene</th>
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</table>
Video cases
**DYT1-TOR1A**

- Oppenheim’s dystonia
- Most common form of genetic dystonia
  - 90% of generalized dystonia in Ashkenazi Jewish (AJ) population
  - 40-60% of generalized dystonia in non AJ population
- Childhood onset (~ age 13), range 1-28 y.
- Almost always (95%) starts in a limb
- 2/3 will progress to generalized or multifocal dystonia
- 20% remain focal dystonia
- Increased rate of recurrent major depression
- Good response to THP and sustained benefit from bilateral GPi DBS

Ozelius L and Lubarr N, GeneReviews, Nov 2016
**DYT1-TOR1A**

- Majority of cases are caused by a 3-base pair deletion (GAG) in exon 5 of *TOR1A*.
- *DYT1* is inherited in an autosomal dominant fashion.
- However, there is reduced penetrance of 30%.
- *TOR1A* encodes a nuclear envelope heat shock protein in the AAA+ ATPase family (torsinA).

- THAP1 (*DYT6*) binds to the *TOR1A* promoter and decreases its expression.

Video case
DYT6-THAP1

- Age of onset ~16.1 – 24 y. (5-38 y.)
- 50% present as cranial or cervical dystonia
- Prominent laryngeal involvement
- Frequent progression to involve multiple body regions
- Autosomal dominant inheritance with 60% penetrance
- Two homozygous families have been described
- Founder effect in the Amish-Mennonites
- > 50 mutations described across populations
- Explains 1-2% of all idiopathic dystonia cases

Video cases
Dopa responsive dystonia

**GTPCH1**

- **Clinical presentation**
  - Mean age of onset 5-8.5 y. (0-54)
  - Male: Female 1 : 2.5-4
  - Limb onset dystonia leg>> arm, equinovarus posturing
  - Brisk DTRs and ankle clonus
  - Diurnal fluctuation
  - Improvement on low dose L-dopa
  - Mild Parkinsonism in particular in adult onset

- **Non motor symptoms**
  - Depression, anxiety, OCD possibly due to low 5-HT levels
  - Excessive sleepiness, nightmares
  - Normal to borderline intellectual functioning

DYT5-GTPCH1

- Treatable form of genetic dystonia
- AD form
  - Most common DRD
  - Prevalence 0.5 to 1 per million
  - Penetrance 38% vs 87%; Male: Female 1:2.5-4
  - >100 mutations in gene including large indels of chr. 14q22.1–14q22.2
- AR form
  - More severe phenotype with spasticity and oculogyric crisis
  - Neonatal hyperphenylalaninemia
  - Possibly requires higher doses of L-dopa

The dopamine pathway

Trendler-Gerhard, J Neurol Neurosurg Psychiatry 2009

L-dopa trial
- < 6 yo: 1-10 mg/kg/day
- > 6 yo: 50 mg TID x 1 week and slowly increase to 200 mg TID
- Response should be evaluated after 1 month
- Typical patients have good response with 50–200 mg levodopa daily
- Dyskinesias /fluctuations infrequent in GTPCH1
- Safe during pregnancy
- Lumbar puncture and/or genetic testing

Video cases
**DYT12-ATP1A3**

- *ATP1A3* encodes the Na+/K+ ATPase alpha 3 subunit
- Mutations in *ATP1A3* cause a spectrum of disorders
  - rapid onset dystonia parkinsonism (RDP)
  - alternating hemiplegia of childhood (AHC)
  - cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss (CAPOS) syndrome
  - epileptic encephalopathy
  - relapsing encephalopathy with cerebellar ataxia
  - rapid adult onset ataxia
  - CAPOS with hemiplegic migraine

RPD

- Rapid-onset dystonia parkinsonism
- Sudden onset of dystonic posturing, postural instability and/or bradykinesia over hours to days
- Onset can be triggered by exercise, ETOH, trauma, infection, stress
- Rostro-caudal progression with marked cranial involvement
- Associated with psychiatric disease
- Autosomal dominant transmission

Genotype-phenotype correlation

Figure 3: Density plot showing the distribution of AHC and RDP mutations in ATP1A3
Chorea

- Chorea refers to brief involuntary movements of limbs, trunk, neck, or face that rapidly travel from region to region in an irregular, flowing, nonstereotyped pattern.
Child/infant, not Sydenham’s

Inheritance

Autosomal dominant
- GLUT1 deficiency (decreased glucose CSF/serum ratio)?
  - PRRT2 mutation?
  - Paroxysmal, yes
  - no

Benign, hereditary chorea
- Appropriate work-up - serum/urinary organic/amino acids, etc.

Autosomal recessive
- Infantile metabolic diseases?
  - yes
  - MRI Fe+
  - NBIA
  - no

Sporadic
- Post-hypoxic, post-infectious, vascular, calcification, tumor, etc.
- MRI structural lesions
- yes
- no

X-linked
- hyperuremia
  - yes
  - Lesch-Nyhan (males)
  - no
  - „hand-washing movements“
  - yes
  - Rett syndrome (females)

Mitochondriopathy

Intoxication
- Drug-induced
  - Direct side effect
  - Tardive dyskinesia

Metabolic

Autoimmune

Paraneoplastic

CJD new variant
Video cases
Benign Hereditary Chorea

- Autosomal dominant disorder or sporadic mutation
- The most common cause is $TITF1/TTF1/NKX2.1$ gene mutations or large chr. 14q13.3 deletions
- Neurological presentation
  - Onset 2.5-3 y.
  - Motor delay and hypotonia followed by hyperkinetic movements; chorea, dystonia, myoclonus, ataxia
  - Non progressive
  - MRI brain may show anatomical variants

Clinical Spectrum of Benign Hereditary Chorea

**Lung**
- Neonatal/Infant respiratory distress syndrome
- Recurrent pulmonary infection
- Obstructive airways disease
- Chronic interstitial lung disease

**Brain**
- Hypotonia
- Motor developmental delay
- Chorea, Myoclonus, Dystonia, Ataxia
- Dysarthria
- Cognitive impairment
- Psychiatric illness: ADHD, OCD, psychosis

**Brain-Lung-Thyroid**
- Increased risk of lung cancer
- 30%

**Other associated features**
- Malignancy
- Urinary tract abnormalities
- Hypo-/Oligo-dontia
- Short stature
- Webbed neck
- Joint hypermobility
- Hypoparathyroidism
- Sensorineural hearing loss
- Skeletal abnormalities

**Thyroid**
- Congenital hypothyroidism
- Thyroid agenesis
When to suspect *TITF1*

- Childhood onset of hypotonia in association with a hyperkinetic movement disorder plus
  1. Hypothyroidism, neonatal respiratory distress or recurrent respiratory infections (B-T-L triad)
  2. Isolated non-progressive chorea with onset < 5 yo
  3. Childhood onset non-progressive ataxia
  4. Dominant family history of thyroid disease, chorea, ataxia, motor delay, ADHD or psychosis
  5. Mild dysmorphic features: short stature, oligodontia, hypospadias, bulbous nose, CHD
  6. MRI findings of cystic pituitary gland, empty sella, agenesis of corpus callosum

Meijer IA et al, CNS Ohio 2014
ADCY5

- Mutations in *ADCY5* are the second cause of “Benign Hereditary Chorea”.
- *ADCY5* encodes an adenylyl cyclase, which is mainly expressed in the striatum.
- Autosomal dominant inheritance or de novo mutations.
- Over 8 mutations and 27 cases reported.

Chang FCF et al, Movement Disorders 2016, Mencacci N et al, Neurology 2015
Clinical features

- Onset ~ 0-2 y.
- Motor and speech delay, axial hypotonia
- Mixed hyperkinetic movement disorder with characteristic facial chorea-myoclonus
- Pyramidal signs
- Impaired vertical gaze
- Normal or decreased cognition
- Paroxysmal worsening, triggered by stress
- Characteristic hypotonic facial and wide-based, staggering gait with adducted knees
- Phenotype is not benign; CP mimicker

Meijer IA et al, J Child Neur 2016
# Clinical features

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>No. of Cases (Where Reported)</th>
<th>% (n = 20)</th>
<th>% (Where Reported)</th>
<th>Our Series</th>
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<tr>
<td>Presentation</td>
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<td>7 months to 2 years</td>
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<td>37</td>
<td>3/7</td>
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<td>&gt;2 years</td>
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<td>40</td>
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<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>No. of Cases (Where Reported)</th>
<th>% (n = 20)</th>
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<tr>
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Chang FCF et al, Movement Disorders 2016
Mencacci N et al, Neurology 2015
Our patient had significant clinical improvement of dystonia, speech, sialorrhea and gait which translated into improved BFM motor and disability scores at one year and 3 years post op.

Positive responses to stimulation up to 3 years, however long-term efficacy not yet demonstrated
Myoclonus

- Myoclonus is characterized by a sudden, jerky, shock-like movement.
- Positive myoclonus is generated by contraction of muscles due to excitatory inputs.
- Negative myoclonus is defined as the sudden loss of muscle tone (e.g., asterixis).

<table>
<thead>
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<th>Phenomenology</th>
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<td>Distribution</td>
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<td>Hiccups</td>
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<td>Progressive myoclonic epilepsies</td>
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</tr>
<tr>
<td>Other neurodegenerative</td>
<td>Subcortical</td>
</tr>
<tr>
<td>Atypical parkinsonism</td>
<td>Thalamic</td>
</tr>
<tr>
<td>Other basal ganglia degeneration</td>
<td>Brainstem</td>
</tr>
<tr>
<td>Spinocerebellar degeneration</td>
<td>Reticular</td>
</tr>
<tr>
<td></td>
<td>Hyperexplexia (startle)</td>
</tr>
<tr>
<td></td>
<td>Palatal</td>
</tr>
<tr>
<td></td>
<td>Spinal</td>
</tr>
<tr>
<td></td>
<td>Segmental</td>
</tr>
<tr>
<td></td>
<td>Propriospinal</td>
</tr>
<tr>
<td></td>
<td>Peripheral</td>
</tr>
</tbody>
</table>
Video case
Myoclonus Dystonia

- Median age of onset 5-8 y (1.5-18 y)
- Usually presents as truncal and upper limb myoclonus with cervical dystonia and/or writer’s cramp
- In early childhood can present with upper body myoclonus and dystonia OR lower limb dystonia with later onset myoclonus
- Ataxia
- Psychiatric symptoms
  - OCD, anxiety-related disorders, and alcohol dependence
    (Peall KJ et al, Ann Clin Transl Neurol. 2015)

**DYT11-SGCE**

- SGCE mutations explain 50% of individuals with definite M-D
- Single gene mutation vs contiguous gene syndrome
- Autosomal dominant inheritance with variable penetrance
- Penetrance is nearly complete when transmitted by the father because SGCE is maternally imprinted and preferentially expressed from the paternal allele

### SGCE plus syndromes

#### Table 4: Clinical characteristics of cases with contiguous gene deletions involving SGCE

<table>
<thead>
<tr>
<th>Cases</th>
<th>Deletion size (Mb)</th>
<th>Genes involved</th>
<th>Clinical characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>This study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>2.3</td>
<td>PPP1R9A, PEG10, SGCE, CASD1, COLIA2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA1861, CCDC132, HEPACAM2, SAMD9, SAMD9L</td>
<td>Short stature, language delay</td>
</tr>
<tr>
<td>Case 2</td>
<td>2.3</td>
<td>PPP1R9A, PEG10, SGCE, CASD1, COLIA2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA1861, CCDC132, HEPACAM2, SAMD9, SAMD9L</td>
<td>Short stature</td>
</tr>
<tr>
<td>Case 3</td>
<td>2</td>
<td>PEG10, SGCE, CASD1, COLIA2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA1861, CCDC132, HEPACAM2, SAMD9, SAMD9L, CDK6</td>
<td>Intrauterine growth retardation, microcephaly, short stature, joint laxity</td>
</tr>
<tr>
<td>Case 4</td>
<td>1.9</td>
<td>SGCE, CASD1, COLIA2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA1861, CCDC132, HEPACAM2, SAMD9, SAMD9L, CDK6</td>
<td>Microcephaly, short stature, cognitive impairment</td>
</tr>
<tr>
<td>Case 5</td>
<td>0.7</td>
<td>PEG10, SGCE, CASD1, COLIA2</td>
<td>Short stature, psychosis</td>
</tr>
<tr>
<td>DeBerardinis et al.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>9–16.5</td>
<td>SGCE (and contiguous genes, not further defined)</td>
<td>Intrauterine growth retardation, microcephaly, short stature, dysmorphic facies, language delay</td>
</tr>
<tr>
<td>Asmus et al.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>1.63</td>
<td>PEG10, SGCE, COLIA2</td>
<td>Short stature, joint laxity, dental caries, joint laxity, blue sclerae, cerebral cavernous malformations</td>
</tr>
<tr>
<td>Case 2</td>
<td>4.99</td>
<td>PEG10, SGCE, COLIA2, PEX1, KRIT1</td>
<td></td>
</tr>
<tr>
<td>Case 3</td>
<td>8.78</td>
<td>PEG10, SGCE, COLIA2, PEX1, KRIT1, DLX5</td>
<td>Dysmorphic facies, dental caries, cognitive impairment, split-hand split-foot syndrome</td>
</tr>
<tr>
<td>Saugier-Veber et al.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>1.88</td>
<td>SGCE, CASD1, COLIA2, BET1, GNG11, TFP12, GNG1, CALCR, HCTR-6, KIAA1861, CCDC132, HEPACAM2, SAMD9, SAMD9L, CDK6</td>
<td>Intrauterine growth retardation, microcephaly, short stature, joint laxity, cognitive impairment</td>
</tr>
<tr>
<td>Dale et al.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>0.17</td>
<td>SGCE, CASD1</td>
<td>Language delay, cognitive impairment</td>
</tr>
<tr>
<td>Case 2</td>
<td>0.17</td>
<td>SGCE, CASD1</td>
<td>Nil</td>
</tr>
<tr>
<td>Case 3</td>
<td>0.17</td>
<td>SGCE, CASD1</td>
<td>Psychosis</td>
</tr>
</tbody>
</table>

#### B Silver Russell syndrome 2e to maternal uniparental disomy

Myoclonus Dystonia

- **Treatment**
  - Clonazepam
  - Bilateral GPi DBS therapy

- **New myoclonus dystonia genes:**
  - KCTD17 Mencacci NE et al, AJHG 96, 938–947, June 4, 2015
    - More severe dystonia phenotype
  - CACNA1B Groen JL et al Human Molecular Genetics, 2015, Vol. 24, No. 4

Roze E et al, Movement Disorders, Vol. 30, No. 6, 2015,
Conclusion

• This presentation highlights the clinical and genetic complexity of hyperkinetic pediatric movement disorders.
• Genetic diagnosis is important for family counseling and therapeutic considerations.
• Utility of whole exome sequencing in sporadic cases with a complex neurological phenotype in particular in the field of movement disorders.
Questions?
Thank you!

- Dr. T. Pearson (Washington U.) and Dr. N. Lubarr (HackensackUMC)
- Dr. S. Bressman, Dr. Saunders-Pullman and colleagues (Mount Sinai Beth Israel)
- Dr. S. Chouinard (CHUM) and Dr. G. Bernard (MCH)
- American Academy of Neurology Clinical Research Training Fellowship