Update on Dystonia

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Dystonia

Definition:
- **Old definition**: Involuntary sustained contractions of agonist & antagonist muscles, causing twisting movements and abnormal posture
- **New definition**: sustained or intermittent muscle contractions causing abnormal, often repetitive, movements and/or postures

Phenomenology:
- In children:
  - Starts in a limb
  - Rarely starts in the face or neck
  - Typically spreads to the rest of the body to become generalized
- In adults:
  - Starts in the face, neck or limb
  - May spread to nearby muscle group (e.g., neck to the face)
  - Rarely spread to become generalized
Dystonia is a Sign not a Disease

- Virtually, any lesion of the nervous system can induce dystonia
- Numerous etiology of dystonia
- Classification of dystonia has direct implications on:
  - the differential diagnosis
  - the diagnostic work-up
  - the prognosis
  - treatment options
Classification of Dystonia

◆ Traditional Classification:
  ◆ Primary (= idiopathic) dystonia
    ● cause is unknown or a specific genetic mutation causes a neurological disorder whose primary feature is dystonia
    ● Also includes paroxysmal dystonias and dystonia-plus syndromes (e.g., dystonia myoclonus or parkinsonism)
  ◆ Secondary dystonia
    ● cause of the dystonia can be readily identified

◆ New Classification
  ◆ Axis 1 addresses the clinical characteristics of dystonia:
    ● age at onset, body distribution, temporal pattern and associated features
  ◆ Axis 2 addresses the etiology of dystonia:
    ● degenerative vs non-degenerative forms at the gross, microscopic, or molecular level
    ● inherited vs acquired forms
Primary Dystonias

Dystonia of unknown cause

Dystonia with DYT gene mutation*

- DYT 1: early-onset primary torsion dystonia
- DYT 2: early-onset primary dystonia with prominent cranio-cervical involvement
- DYT 3: adult onset dystonia-parkinsonism (prevalent in the Philippines)
- DYT 4: Whispering dystonia (adult onset spasmodic dysphonia) with generalization and ‘hobby horse’ gait
- DYT 6: adult-onset torsion dystonia with prominent cranio-cervical and laryngeal involvement
- DYT 7: adult-onset primary cervical dystonia
- DYT 12: rapid onset dystonia parkinsonism and alternating hemiplegia of childhood
- DYT 13: early onset torsion dystonia (in one Italian family)
- DYT 16: early-onset dystonia-parkinsonism
- DYT 17: primary focal dystonia with progression (in one Lebanese family)
- DYT 21: adult-onset mixed dystonia with generalization
- DYT 23: cranio-cervical dystonia, often tremulous, with/without upper limb tremor

Dystonia-plus syndromes

dopa-responsive dystonia

- Progressive dopa-responsive dystonia with diurnal variation due to DYT 5a gene mutation
- Akinetic rigid syndrome with dopa-responsive dystonia or complex encephalopathy due to DYT 5b gene mutation

myoclonus-dystonia syndrome due to a DYT 11 and DYT 15 gene mutation

rapid-onset dystonia parkinsonism syndrome due to DYT-12 gene mutation

Paroxysmal dystonias

- paroxysmal non-kinesigenic dystonia due to DYT 8 and DYT 20 gene mutation
- paroxysmal kinesigenic dystonia due to DYT 10 gene mutation
- paroxysmal exercise-induced dystonia

Paroxysmal exercise-induced dyskinesia with/without epilepsy due to DYT 18 gene mutation

* DYT 9, DYT 14, DYT 19 are synonymous with DYT 18, DYT 5a and DYT 19, respectively. DYT 22 name is reserved but not published.
Secondary Dystonias

Acquired dystonias
   demyelinating brain diseases
   anoxic brain injury
   acute disseminated encephalomyelitis
Infections
   tumors
   Stroke
   Drugs, especially dopamine receptor blocking agents and antiepileptic drugs
   Head trauma

Heredodegenerative dystonias
   Wilson disease
   Huntington disease, Parkinson disease and Parkinson Plus Syndromes
   Dentatorubropallidoluysian atrophy
   Spinocerebellar ataxias (especially spinocerebellar ataxia type 3)
   Errors of metabolism
      Glutaric aciduria
      Methylmalonic academia
      Lesch-Nyhan syndrome
   Lipid storage disorders
      Niemann-Pick disease, Types C and D
      GM1 and GM2 gangliosidoses
      Ceroid lipofuscinoses
   Mitochondrial disorders
   Neuronal degeneration with brain iron accumulation, including pantothenate kinase associated neurodegeneration
DYSTONIA

PRIMARY

- Focal
  - Cranial dystonia:
    - Blepharospasm
    - Facial dystonia (Meige syndrome)
    - Jaw dystonia
    - Spasmodic dysphonia
    - Spasmodic torticollis
  - Trunk dystonia (scoliosis)
  - Limb dystonia
  - Task-specific dystonia
    - Writer’s cramp
    - Musician dystonia

- Generalized
  - Dopa-responsive Dystonia
  - DYT 1, 2, … 23
  - Paroxysmal dystonia

- Hereditary
  - Wilson disease
  - Huntington disease
  - DRPLA
  - SCA
  - Storage disease
  - Mitochondrial disease
  - NBIA

SECONDARY

- Acquired
  - Demyelinating disease
  - Perinatal anoxia
  - Encephalitis
  - Infections
  - Tumors
  - Stroke
  - Drugs (acute and tardive dystonia)
  - Head trauma
Diagnosis of Dystonia

- **History:**
  - Establish age at onset, pattern and progression of the dystonia, the family history, and the associated neurological symptoms (such as tremor, pain...)
  - Video from caregiver for paroxysmal dystonias

- **Physical exam:**
  - Observe dystonic movements and postures
  - Associated neurological signs (such as parkinsonism and myoclonus)

- **Imaging of brain and/or spine to rule out:**
  - Anatomical lesions, metal or calcium deposition, caudate atrophy, white matter changes...

- **Blood, urine, and cerebrospinal fluid amino acid levels in children**

- **Abnormal CSF glucose, lactate, and pyruvate point to a mitochondrial disorder (may be confirmed by genetic testing or a muscle biopsy)**

- **Nerve conduction studies rule out neuropathy (such as in spinocerebellar ataxia, neuroacanthocytosis, or metachromatic leukodystrophy)**
Treatment of Dystonia: Nothing Proven!

◆ Start low & go slow

◆ Treatment of primary dystonia:
  ▪ Levodopa for generalized dystonia, especially in children
  ▪ Baclofen
  ▪ Benzodiazepines: clonazepam
  ▪ Anticholinergic drugs (mostly for children)
    ● watch for cognitive adverse effects
  ▪ Dopamine depleters: tetrabenazine, (reserpine)
    ● Watch for suicidal depression, hypotension, parkinsonism
  ▪ Dopamine receptor blockers: pimozide, haloperidol

◆ For focal dystonia:
  ▪ Botulinum toxin cleaves polypeptides essential for the docking of synaptic vesicles to the pre-synaptic membrane
    ● Reversible chemical denervation of the injected muscles
    ● In adults: up to 300-400 units every 3 months
    ● In children: 10 units/kg, some tried 15-25 units/kg (Willis 2007)
    ● One unit of Botox™ is equivalent in potency to 1 unit of Xeomin™, 3–4 unit of Dysport™ & 50 unit of Myobloc™/NeuroBloc™ (type B)
Treatment of Dystonia

- Treatment of secondary dystonia:
  - Treating the underlying cause if possible
    - In tardive dystonia: discontinue dopamine receptor blocking agent
    - In Wilson disease: copper restriction and chelators
  - Anti-dystonic drugs like Rx of primary dystonia

- For intractable dystonia:
  - Deep brain stimulation of the GPi
    - Inconsistent benefit from DBS therapy
    - In general, secondary dystonias are less responsive to drug and DBS therapy than primary dystonias (?)
    - STN DBS may be useful too

- Physical therapy
  - prevent contractures, mobilize joints, and optimize motor function
  - assistive devices such as customized braces, electric wheelchairs, and communication devices
Status Dystonicus (Dystonic Storm)

- **Definition:** severe episodes of exacerbation of generalized dystonia
  - in the context of primary or secondary dystonia
  - life-threatening neurological emergency
  - painful dystonic muscle spasms may lead to:
    - respiratory compromise
    - metabolic complications (hyperpyrexia, dehydration, respiratory failure, and rhabdomyolysis)

- **Triggers:**
  - No obvious trigger
  - infections, reduction of lithium dose, tetrabenazine withdrawal and the introduction of clonazepam, penicillamine or zinc therapies

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<thead>
<tr>
<th>For acute treatment of status dystonicus (dystonic storm)</th>
<th>Midazolam</th>
<th>Propofol</th>
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</thead>
<tbody>
<tr>
<td>0.05 mg/kg iv injection over 2–3 min, followed by 0.03 mg kg⁻¹ h⁻¹ (0.5 mcg kg⁻¹ min⁻¹) iv drip</td>
<td>Increase every 5 min by 25% of the current infusion rate, up to 0.12 mg kg⁻¹ h⁻¹ (2 mcg kg⁻¹ min⁻¹)</td>
<td>Increase by 0.3 mg kg⁻¹ h⁻¹ every 5–10 min, up to 0.5–3 mg kg⁻¹ h⁻¹</td>
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In extreme instances:
- Barbiturate anesthesia
- Intrathecal baclofen
- GPi DBS therapy

Tabbal, Curr Treat Options Neurol, 2015
Acute Dystonic Reaction

Caused by acute intake of dopamine receptor blocking agents

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<th>For treatment of acute dystonic reaction induced by dopamine receptor blocking agents</th>
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<tbody>
<tr>
<td>Benztropine</td>
<td>0.02–0.05 mg/kg im or iv</td>
<td>0.02 to 0.05 mg/kg orally twice per day for 1 to 3 days (maximum 2 mg per dose)</td>
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<tr>
<td>Diphenhydramine</td>
<td>1–1.25 mg/kg im or iv</td>
<td>1–1.25 mg/kg orally every 6–8 h for 1–3 days without exceeding 50 mg per dose</td>
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Tabbal, Curr Treat Options Neurol, 2015
Tardive Dyskinesia & Dystonia

◆ **Etiology:**
  - Chronic (>3 months) D2-dopamine receptor blocking agents (neuroleptics or anti-emetic drugs) resulting in chorea and/or dystonia
  - Quetiapine and clozapine do NOT cause tardive syndromes

◆ **Phenomenology:**
  - Choreic/dystonic repetitive movements of the face, lips and tongue (sometimes jaw, limbs, respiratory muscles...)
  - May become IRREVERSIBLE in 1/3 of instances
    - Especially in elderly or in patients with pre-existing brain lesions

◆ **Treatment:**
  - Discontinue D2-dopamine receptor blocking agents
  - Baclofen
  - Benzodiazepines: clonazepam
  - Anticholinergic drugs for dystonia, but may worse dyskinesia
  - Dopamine depleters: tetrabenazine, (reserpine)
Paroxysmal Dystonia/Dyskinesia

◆ Paroxysmal kinesigenic dyskinesia (PKD):
  - Typically responsive to anticonvulsants, particularly phenytoin, carbamazepine and valproate
  - Required doses for the control of the paroxysms are generally lower than those required for the treatment of seizures

◆ Paroxysmal non-kinesigenic dyskinesia (PNKD):
  - Poorly responsive to drug therapy (such as anticonvulsants)
  - Partial response to anticholinergic drugs, levodopa, acetazolamide, carbamazepine, haloperidol, gabapentin and clonazepam
Wilson Disease

◆ Autosomal recessive hereditary disease on chromosome 13q14.3:
  ▪ Codes for a P-type (cation transport enzyme) ATPase
  ▪ Transports copper into bile and incorporates it into ceruloplasmin
  ▪ Expressed primarily in the liver, kidney and placenta
  ▪ Onset before 45 years

◆ Pathology:
  ▪ Copper deposition in basal ganglia and liver and limbus of cornea (Kayser-Fleischer rings)

◆ Phenomenology:
  ▪ Neurologic: tremor, dystonia, cerebellar signs, parkinsonism
  ▪ Psychiatric: dementia, behavioral disturbances
  ▪ Liver failure

◆ Treatment:
  ▪ Copper restriction & chelators (penicillamine, trientine…)
  ▪ Symptomatic treatment of motor manifestations
Dopa-Responsive Dystonia

- Most commonly caused by mutations in the GCH1 gene on chromosome 14 resulting in guanosine triphosphate (GTP) cyclohydrolase I deficiency

- Over 100 different mutations have been identified

Phenomenology:
- Onset: usually at 4-8 years of age
- Foot or arm dystonia, then generalized
- 50% have worsening of Sx late in the day (diurnal rhythm)

Treatment: Perfect!
- Low dose levodopa (100-600 mg/day)
  - Excellent respond to levodopa for life
  - do not develop motor fluctuations like those in Parkinson disease
- (Anticholinergic drugs)
Metabolism of Dopamine & Serotonin

- **Guanosine triphosphate (GTP)**
  - GTP-cyclohydrolase I (GCH-I)*
  - Dihydroneopterin triphosphate
    - 6-pyruvoyl-tetrahydropterin synthase*
  - 6-pyruvoyl-tetrahydropterin (PTP)
    - Sepiapterin reductase*
  - 6-lactoyl-tetrahydropterin (dihydrosepiapterin)
    - Sepiapterin reductase*
  - Tetrahydrobiopterin (BH4)

- **Phenylalanine**
  - Phenylalanine hydroxylase
  - Tyrosine hydroxylase* (BH4)
  - Tyrosine
    - Aromatic L-amino acid hydroxylase*
  - Dopa
    - Aromatic L-amino acid hydroxylase*
  - Dopamine
  - Tryptophan hydroxylase
    - Tryptophan hydroxylase (BH4)
  - Tryptophan
    - 5-hydroxytryptophan (5-HTP)
    - Aromatic L-amino acid hydroxylase*
  - Serotonin

* = enzymes whose deficiency have been described to manifest as dopa-responsive dystonia

Tabbal, Curr Treat Options Neurol, 2015
Conclusions

◆ Dystonia is a manifestation of multiple diseases of various etiologies

◆ Treatment of dystonia relies on:
  ▪ accurately identifying the type and etiology of the dystonia
  ▪ Trials of multiple medications using a slow titration schedule to achieve the lowest effective dose while minimizing adverse effects

◆ Current treatment options for primary dystonia address symptoms rather than the pathophysiology of the disease

◆ Novel therapies will rely on further understanding the pathophysiology of dystonia, spearheaded by:
  ▪ discovery of multiple DYT genes
  ▪ development of several animal models, including primate models of dystonia