Dystonias

Etiological Classification Of Dystonia

I. DOPATHIC (PRIMARY) DYSTONIA

A. Sporadic (idiopathic torsion dystonia, ITD)
B. Inherited (hereditary torsion dystonia)

1. Classic autosomal dominant dystonia (DYT1 gene, 9q34)
2. Nonclassic autosomal dominant dystonia (not DYT1 gene)
3. Autosomal recessive dystonia (tyrosine hydroxylase deficiency)

II. SECONDARY DYSTONIA - known pathological cause

A. Dystonia-plus syndromes - forms of primary dystonia associated with additional neurological deficits

1. Myoclonic dystonia (not DYT1 gene)
2. Dopa-responsive dystonia (DRD)
3. Rapid-onset dystonia-parkinsonism (RDP)
4. Early-onset parkinsonism with dystonia (EPD)
5. Paroxysmal dystonia-chorrethathelosis

B. Associated with neurodegenerative disorders

1. Sporadic
   - Parkinson's disease
   - Progressive supranuclear palsy
   - Multiple system atrophy
   - Corticobasal ganglionic degeneration
   - Multiple sclerosis
   - Central pontine myelinolysis

2. Inherited
   - Wilson's disease
   - Huntington's disease
   - Juvenile parkinsonism-dystonia
   - Progressive pallidal degeneration
   - Hallervorden-Spatz disease
   - Hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration (HARP syndrome)
   - Joseph's disease
   - Ataxia telangiectasia
   - Neuropathy-ataxia syndrome
   - Retts syndrome (?)
   - Intracranial inclusion disease
   - Infantile bilateral striatal necrosis
   - Familial basal ganglia calcifications
   - Spinoocerebellar degeneration
   - Olivopontocerebellar atrophy
   - Hereditary spastic paraplegia with dystonia
   - X-linked dystonia-parkinsonism or Lubag (pericentricrome)

Deletion of 18q

C. Associated with metabolic disorders

1. Amino acid disorders
   - Glutaric acidemia
   - Methylmalonic acidemia
   - Homocystinuria
   - Hartnup's disease
   - Tyrosinosis

2. Lipid disorders
   - Metachromatic leukodystrophy
   - Cerebrotendinous xanthomatosis
   - Dystonic lipidoses ("sea blue" histiocytosis)
   - Gangliosidoses GM1, GM2, GM3 variants
   - Hexitasemias A and B deficiencies

3. Miscellaneous metabolic disorders
   - Wilson's disease
   - Mitochondrial encephalopathies: Leigh's disease, Leber's disease
   - Lesch-Nyhan syndrome
   - Triosephosphate isomerase deficiency
   - Vitamin E deficiency
   - Biotin deficiency
   - Astrovirus infection

D. Due to known specific cause

Drugs
- antipsychotics (tardive dystonia), levodopa, bromocriptine, metoclopramide, flunarizine, flunarizine, reboxetine, certain calcium channel blockers
- Perinatal cerebral injury and keni-intrinsic atresia cerebral palsy, delayed onset dystonia
- Infection: viral encephalitis, encephalitis lethargica, Reyss's syndrome; subacute sclerosing panencephalitis, Creutzfeldt-Jakob disease, AIDS
- Other: tuberculosis, syphilis, acute infectious torticollis
- Penicillamine brain stem encephalitis
- Cerebral vascular and ischemic injury
- Brain tumor
- Atrioventricular malformation
- Head trauma and brain surgery
- Peripheral trauma (e.g. focal dystonia in afflicted region)
- Torsion: MN, CO-CSS: methanol, disulfiram, wasp sting

III. OTHER HYPERKINETIC SYMPTOMS ASSOCIATED WITH DYSTONIA

A. Tic disorders with dystonic tics
Psychogenic
Symptomatic (secondary) dystonia
DOPA
N.B.
Burke
7.
6.
5.
4.
3.
2.
1.
PREVALENCE
B.
A.
V.
IV.
B.
DIFFERENTIAL DIAGNOS
Paroxysmal dyskinesias
P
I
S
enhanced excitability.
structural /
altered physiological control of descending pathways
among
clinics.
2
Primary dystonia
Younger
generalized).
Primary dystonia is almost always focal or segmental).
Expression of gene is highly variable (even within families)
 PATHOLOGY, PATHOPHYSIOL
no reproducible morphological or biochemical abnormalities are identified!!
altered physiological control of descending pathways from basal ganglia and brain stem.
e.g. HEMIDYSTONIA results from lesion in contralateral striatum (particularly putamen).
PATHOLOGY, PATHOPHYSIOLOGY

CLINICAL FEATURES
see p. Mov1 >>
1. Expression of gene is highly variable (even within families) – dystonia may be generalized (17%), segmental (33%) or only focal (50% of all cases).

2. Secondary dystonia begins as focal condition (and may sequentially progress to segmental – generalized).
– in children-onset dystonia legs and feet* are most commonly initially affected.
  – e.g. peculiar leg twisting and foot inversion when child walks forward, even though walking backward, running, or dancing may still be normal.
– adult-onset dystonia usually begins in arms (writer's cramp), neck (torticollis), face (blepharospasm), jaw (oromandibular dystonia), tongue (lingual dystonia), or vocal cords (spastic dysphonia); not in legs!
N.B. adult-onset dystonia is six times more common!

3. Younger age at onset, more likely dystonia is to become generalized and disabling (adult-onset primary dystonia is almost always focal or segmental).
– rate of progression is extremely variable (usually greatest within first 5-10 years → static phase).

4. Environmental conditions affect dystonia; dystonic signs become prominent in later part of day.

5. During disorder progression: task-specific dystonia → action dystonia → overflow dystonia → continual dystonia (dystonia at rest) → fixed postures

6. Muscles tone & power are normal, but involuntary movements interfere with function and make voluntary activities extremely difficult.

7. Mental activity, sensations, tendon reflexes remain normal.

SCALES
Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS)

DIAGNOSIS
structural / functional imaging - no discernible abnormalities can be identified.
abnormal results of blink, acoustic, vestibulo-ocular reflex testing - brain stem reflexes have enhanced excitability.
N.B. ceruloplasmin level should be obtained in all patients in whom dystonia occurs before age of 50!

DIFFERENTIAL DIAGNOSIS
DOPA-responsive dystonia see below >>
Symptomatic (secondary) dystonia - additional neurologic deficits, possible etiologic factors.
Psychogenic dystonia – has suggestive clues:
– abrupt onset as paroxysmal disorder with fixed posture.
– inconsistent movements (changing characteristics over time).

PRIMARY DYSTONIA (s. dystonia musculorum deformans, idiopathic torsion dystonia)
A. SPORADIC (idiopathic torsion dystonia, ITD)
B. INHERITED (hereditary torsion dystonia):
  1. CLASSIC autosomal dominant ITD (DYT1 gene, 9q34)* - most childhood- and adolescent-onset cases (formerly known as dystonia musculorum deformans).
  – three base pair deletion in DYT1 gene on 9q22-34 (coding for ATP-domain protein torsin A).
  2. NONCLASSIC autosomal dominant ITD (not DYT1 gene)
  3. Autosomal recessive dystonia hyperdystrophy / dystonia hyperreflexia / hyperkinesia
  4. X-linked recessive (Xq21.3).

PREVALENCE: 3.4-3.0 per 100,000 population;
• 2nd most commonly encountered movement disorder (after parkinsonism) in movement disorder clinics.
• among Ashkenazi Jews prevalence is at least double!
incongruous movements (do not fit with recognized pattern or with normal physiologic patterns)

- additional types of abnormal movements that are not consistent with basic abnormal movement pattern or are not congruous with known movement disorder.
- movements disappear with distraction.
- response to placebo, suggestion, psychotherapy.
- spontaneous remissions.

N.B. because of fluctuations in severity, sometimes influenced by emotional state of patient. primary dystonia is often mistakenly attributed to psychogenic causes.

TREATMENT

1. High-dose ANTICholinERGICS (e.g. TRIBUSYMPHENIDIL [Artane®] up to 70 mg/d) - most effective symptomatic relief, many patients are unable to tolerate such high doses.

2. High-dose BACLOFEN

3. BENZODIAZEPINES (CLONAZEPAM, LORAZEPAM, DIAZEPAM)

4. CARBAMAZEPINE

5. ANTIDOPAMINERGICS (reserpine, dopamine receptor blockers).

Childhood-onset dystonia → trial of LEVODOPA (is not to overlook DOPA-responsive dystonia).

Generalized and axial dystonia → intrathecal BACLOFEN (controlled trials have not been published).

Focal, segmental dystonia → intramuscular injections of BOTULINUM TOXIN TYPE A q 3-5 months. - some clinicians perform with EMG guidance - some patients develop resistance (antibodies to toxin).

- most efficient in CERVICAL dystonia.
- also can be used for generalised dystonia (injections into most severely affected focal site).

Surgical procedures - effective in major but high rates of recurrence. see p. Op360

1) pathidal DRN (FDA approved) - not a cure, but long-term therapy whose efficacy doesn't wane significantly.

2) thalamotomy - useful in unilateral dystonia (most effective for resting, extremites dystonia); bilateral thalamotomy carries 20% risk of dysarthria!

3) cervical cord stimulation

4) rhizotomy, peripheral nerve section (denervation), myotomy – for focal / segmental dystonias.

MOST COMMON FORMS OF FOCAL DYSTONIA

CERVICAL DYSTONIA & SPASMODIC TORTICOLLIS - most common focal dystonia!

• occurs at all ages (usually 20-60).

CLINICAL FEATURES

• any bilateral combination of neck muscles can be involved → sustained turning / fisting / flexing / extending neck, shifting head laterally or anteriorly (e.g. torticollis, laterocollis, anterocollis, retrocollis).

- shoulder is elevated and anteriorly displaced on side to which chin turns.

N.B. some neck muscles contract in compensation for movements of primary agonists (sometimes difficult to decide which muscles to inject with botulinum toxin).

- instead of sustained head deviation, some have jerking head movements (50% have associated head-neck tremor).

- neck pain (occurs in 2/3) - responds to botulinum toxin at site of pain or steroid injections (e.g. at greater occipital nerve), e/o dysarthria complicates cervical dystonia in ~ 20%.

- common sensory trick may relieve cervical dystonia. see p. Mov1

- 10% have remission within year of onset → relapse years later.

Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS):

Torticollis severity scale (max 35 points)

Disability scale (max 30 points)

Pain severity scale (max 20 points)

DIFFERENT FORMS OF DYSTONIA

1) congenital contracture of sternocleidomastoid muscle; H: surgical release.

2) SANDIFER syndrome - extreme head tilt caused by gastroesophageal reflux in young boys after full meal; H: plication surgery

3) CN 4 palsy

4) malformations - Arnold-Chiari; cervical spine (e.g. Klippel-Feil fusion, atlantoaxial subluxation)

5) cervical infections, trauma

6) tumor in posterior fossa

7) spasms from cervical muscle shortening.

8) BENIGN PAROXYSMAL TORTICOLLIS - recurrent attacks of head tilt associated with palsy, agitation, vomiting.

- onset at 2-8 months of age; spontaneous remission by 2-3 yr of age.

- during attack, child resists passive head movement.

- abnormalities in vestibular function (as in benign paroxysmal vertigo).

MEDICAL TREATMENT

ABOTULINUMTOXIN A (DYSport®) - first choice for treatment of adults with cervical dystonia (both toxin-naive and previously treated patients)

INTRATRACHEAL TOXIN A (Zemaira®) - FDA approved botulinum toxin type A for treatment of adults with cervical dystonia or blepharospasm.

Surgical Treatment

DHN (Bilater al, GPi) - for botulinum toxin refractory cases.

MICROTUBULAR DCONCEPTION (MVD) of CN11 at cervicomедullary junction – for local vascular compression – manifests as Cervical rotary torticolli during upright or recumbent position.

SELECTIVE CEREBRAL ANTERIOR RHIZOTOMY

1) bilateral C1-C3 anterior rhizotomy

2) C4 anterior rhizotomy ipsilateral to side of head turning.

3) posterior rami of C5-7 roots on side of C1-C4 anterior rhizotomy + posterior rami of C4-7 roots on opposite side, may be coagulated (where they pass around associated cervical facet joint) - further denervates posterior paraspinal muscles.

- sternocleidomastoid muscle is transected at midbelly.

- branches of CN11 are stimulated to identify sternomastoid branch, which is then transected.

- high intradural CN11 transection will produce only partial denervation of sternomastoid and trapezius muscles.
**DYSTONIA**

- Selective Myotomies:
  - scalene muscles are transected in anteflexional or lateroflexional torticollis (scalene muscles are innervated by lower cervical roots which cannot be transected without producing paresis of upper extremity).
  - pure retrocollis - unilateral resection of splenius and semispinalis muscles.

Aggressive physical therapy is necessary postoperatively.

**BLEPHAROSPASM**

- involuntarily forceful spasmodic contraction of orbicularis oculi muscle leading to visual dysfunction.
  - etiology - unknown.
  - women > men; usually > 50 yrs.
  - may occur in isolation – focal dystonia.
  - Merje syndrome - association with other cranial, cervical & laryngeal dystonias – i.e. segmental craniofacial dystonia.

**CLINICAL FEATURES**

- initiated / aggravated by emotion, stress, fatigue, drugs, bright light.
- preceded by exaggerated blinking.
- starts unilaterally, becoming bilateral.
- various tricks (gestes antagonistes) may reduce blepharospasm (e.g. touching just lateral to orbit, pulling eyelids).
- severe untreated cases result in functional blindness.

**TREATMENT**

1. anticholinergics (e.g. BENZHEXOL).
2. orbicularis myectomy
3. BOTULINUM TOXIN TYPE A (BOTOX) injections into orbicularis oculi muscle; repeated q 3 months.

**WRITER’S CRAMP**

- task-specific focal dystonia.
  - may spread to other arm (cramp of adult onset usually remains limited to one limb).
  - patient should learn to write with nondominant hand.
  - bilateral involvement or if dystonia affects other activities (buttoning, shaving, playing musical instrument) → botulinum toxin injections.

**DYSTONIA OF VOCAL CORDS**

1. SPASTIC (SPASMATIC) DYSPHONIA (more common type) - vocalis muscles contract bringing vocal cords together → voice is restricted, strangled, coarse, often broken up with pauses.
   - often is associated with tremor of vocal cords.
   - H: botulinum toxin injections

2. BREATHY (WHISPERING) DYSPHONIA - contractions of posterior cricoarytenoids (abductors of vocal cords) → patient cannot talk in loud voice and tends to run out of air while trying to speak.
   - botulinum toxin injections are uncertain.

**DYSTONIA-PLUS SYNDROMES**

**DOPA-RESPONSIVE DYSTONIA**

- 10% cases of childhood-onset dystonia.
- autosomal dominant GTP cyclohydrolase 1 gene (14q22.1-q22.2) defect → defect in dihydrobiopterin synthesis.
- pathophysiology - normal numbers of hypopigmented substantia nigra neurons, no Lewy bodies; reduced striatal dopamine.
- begins at age 6-16 yrs.
- DYSTONIA + PARKINSONISM without progression.
- hyperreflexia (particularly in legs, sometimes with extensor plantar responses).
- marked diurnal fluctuations: symptom-free in early morning → worsening as day wears on → virtually crippled by evening.
- PET – normal.
- remarkable therapeutic response to low doses of LEVODOPA, dopamine agonist, or anticholinergic drug.

N.B. all children with dystonia and adults with leg or trunk dystonia deserve trial of LEVODOPA!

**MAJOR DIFFERENTIAL DIAGNOSIS**

<table>
<thead>
<tr>
<th>Juvenile Parkinson Disease</th>
<th>DOPA-responsive Dystonia</th>
<th>Childhood Idiopathic Torson Dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Onset</td>
<td>Rare &lt; 8 yrs.</td>
<td>Infancy = 12 yrs.</td>
</tr>
<tr>
<td>Gender</td>
<td>Predominantly male</td>
<td>Predominantly female</td>
</tr>
</tbody>
</table>
Dystonia

<table>
<thead>
<tr>
<th></th>
<th>Juvenile Parkinson Disease</th>
<th>DOPA-responsive Dystonia</th>
<th>Childhood Idiopathic Torsion Dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Sign</td>
<td>Foot dystonia or PD</td>
<td>Foot and leg dystonia</td>
<td>Arm or leg dystonia</td>
</tr>
<tr>
<td>Dystonia</td>
<td>At onset</td>
<td>Throughout</td>
<td>Throughout</td>
</tr>
<tr>
<td>Diurnal variation</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pull Test</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>Gait</td>
<td>Abnormal</td>
<td>Abnormal</td>
<td>Abnormal if leg or trunk is affected</td>
</tr>
<tr>
<td>“OFF” Episodes</td>
<td>Fluctuations</td>
<td>Stable</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dyskinesias</td>
<td>Prominent</td>
<td>Uncommon</td>
<td>Unknown</td>
</tr>
<tr>
<td>Fluorodopa PET</td>
<td>Decreased</td>
<td>Slight decrease</td>
<td>Normal</td>
</tr>
<tr>
<td>DOPA Responsive (Dosage)</td>
<td>Yes (moderate to high)</td>
<td>Yes (very low)</td>
<td>No, or mild (high)</td>
</tr>
<tr>
<td>Anticholinergic Response</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>Progressive</td>
<td>Plateaus</td>
<td>Usually worsens</td>
</tr>
</tbody>
</table>

**X-LINKED DYSTONIA-PARKINSONISM**

- confined largely to Philippines.
- patients, mostly men, develop severe axial dystonia and hunched parkinsonian posture.
- falls, dysphagia, and voice compromise are preludes to death.

**BIBLIOGRAPHY** for ch. “Movement disorders, Ataxias” — follow this [LINK] >>