Diagnosis and treatment of dystonia

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What is dystonia?

- Disorder of movement characterised by involuntary sustained muscle contractions
- Twisting and repetitive movements or abnormal postures
- Movements typically patterned and may be tremulous
- Action induced and may be associated with overflow muscle activation
- Abates during sleep
- Affect many parts of the body
  - neck, eyes, limbs, larynx, mouth and tongue
- Abnormal processing of motor commands
- Dystonia is a clinical diagnosis
1897: Barraquer-Roviralta – patient with “athetosis”
1908: Schwalbe described three siblings with generalised motor disorder
1911 Oppenheim coined term dystonia
1911 Flatau - first description of autosomal dominant DYT1 dystonia
1944: Herz defined entity of primary dystonia
1970s: Marsden linked generalised forms with focal forms
1980s: Fahn refined phenotypes
2013: Consensus on phenomenology and classification
**Axis 1: Clinical Characteristics**

- **Age at onset**
  - Infancy (<2), childhood (3-12), adolescence (13-20), early adult (21-40), late adult (>40)

- **Body distribution**
  - Focal, segmental, multifocal, generalised, hemidystonia

- **Temporal pattern**
  - Disease course:
    - Static, progressive

- **Variability**
  - Persistent, action-specific, diurnal, paroxysmal

- **Associated features:**
  - Isolated, combined
Axis 2: Aetiology

• Nervous system pathology
  – Neurodegeneration
  – Structural lesion
  – Neither
• Inherited or acquired

• Idiopathic
  – Sporadic
  – Familial
Isolated (primary) Dystonia

- Dystonia is sole clinical feature (+/- tremor)
- Various forms:
  - Oppenheim’s dystonia (DYT1 gene)
  - adult onset familial cervical dystonia
  - adult onset cranio-cervical dystonia
  - other familial types
  - sporadic, usually adult onset
DYT1 (Oppenheim’s dystonia): torsinA

Onset age < 28 years
Usually starts in limb
67% progress to
generalised/multifocal
dystonia over 5-10 years
25% involve trunk and neck,
cranial muscles rarely involved
Caused by GAG deletion in
DYT1 gene
DYT4 Dystonia: beta-tubulin 4A

- Identified in large family with AD whispering dysphonia and generalised dystonia
- Single mutation in beta-tubulin 4a gene
- Autoregulatory domain of protein
- Suggests involvement of neuronal cytoskeleton
DYT6 Dystonia: THAP1

- Originally described in 2 Mennonite families
- Autosomal dominant
- Mixed phenotype
- Early or adult onset in limb, cervical or cranial muscles
- Phenotype of AD generalised dystonia, involving neck and face with predominant laryngeal spasm
- A few sporadic cases also reported
Other DYT familial phenotypes

- DYT2: AR: Spanish Gypsies and Sephardic Jewish family. Generalised +/- craniocervical involvement
- DYT7: AD: German family with focal dystonia.
- DYT13: Onset 1\textsuperscript{st} 2 decades. Upper body (neck and arm)
- DYT21: AD: generalised/ multifocal dystonia often starting with blepharospasm
- DYT23 (\textit{C1Z1}): AD cervical dystonia
- DYT24 (Anoctamin3): AD craniocervical dystonia.
- DYT25 (\textit{GNAL}): AD Cervical and segmental dystonia
Primary focal dystonia

- Adult onset
- Cervical dystonia (spasmodic torticollis)
- Blepharospasm
- Writer’s cramp
- Oromandibular dystonia
- Laryngeal dystonia
- Task specific dystonias: musicians cramps, typists cramps etc
- In general do not spread (BSP 31%, CD 9%, LD 12%, WC 16%)
- Sensory tricks (geste antagoniste)
- Worsened by fatigue and emotional stress
- Can be associated with pain (especially cervical dystonia)
Combined Dystonia: Dopa-responsive dystonia

- 5% inherited dystonia, autosomal dominant
- Onset in childhood, usually limb with spread
- Diurnal variation
- Adult focal dystonia or parkinsonism
- Atypical cases - spastic paraparesis, cerebral palsy, OMD, spontaneously remitting dystonia
- Profound response to levo-dopa
- Important to differentiate from early onset parkinsonism caused by Parkin gene mutations
- Most cases caused by mutations in GCH1 gene
Combined Dystonia: Myoclonus-dystonia

- Autosomal dominant
- 1<sup>st</sup> or 2<sup>nd</sup> decade onset of myoclonus
- Predominantly in upper limbs and trunk
- Usually with mild dystonia: neck, face, arms
- Alcohol and benzodiazepine sensitive
- Associated with psychological disturbance: panic attacks, OCD
- Caused by mutations in epsilon-sarcoglycan gene
Combined Dystonia: Rapid-onset dystonia-Parkinsonism

- Described in small number of families
- Autosomal dominant inheritance
- Acute/subacute onset in adolescence (range 8-55 years)
- Mild antecedent limb symptoms
- Rostrocaudal progression of symptoms
- Dystonia with prominent dysarthria and dysphagia, grimacing, bradykinesia, postural instability and hyper-reflexia
- Symptoms plateau and refractory to treatment
- Caused by mutations in ATP1A3 gene
Dystonia secondary to nervous system pathology

Drugs/toxins
Perinatal injury
Kernicterus
Trauma
CVA/AVM/tumor
Infectious and post-infectious encephalopathies
Metabolic
Right Cerebellar Arteriovenous Malformation
Dystonia secondary to neurodegeneration

- Autosomal dominant: HD, SCA3
- Autosomal recessive: Wilson’s, NBIA, GM1&2, Parkin
- X-linked: XDP/Lubag, DDP
- Mitochondrial:
- Complex/Unknown:
  Parkinsonism, (PD, MSA, PSP, CBD
“The Rules”

• Isolated (primary) dystonia with young onset usually spreads and is usually genetic
• DYT1 dystonia has onset in limbs with subsequent spread
• Primary dystonia with adult (> 30 years) onset usually remains focal
• Presence of additional neurological features must lead to search for combined dystonia or nervous system (secondary) pathology
• Never forget dopa-responsive dystonia
• All rules can be broken!
Treatment of dystonia

- Oral drugs
  - Levodopa
    - Anticholinergics
      - Baclofen
        - Benzodiazepines
          - Tizanidine, tetrabenazine, etc.
  - Chemodenervation
    - Botulinum toxin A
    - Botulinum toxin B
- Surgical therapies
  - Peripheral surgery
  - Central surgery
    - Selective peripheral denervation
    - Myectomy
    - Deep brain stimulation (globus pallidus)
    - Pallidotomy
- Other treatments
  - Physical and occupational therapy
  - Immobilisation, constraint-induced therapy
Standard symptomatic treatment algorithm for focal dystonia

- Botulinum toxin
- Anticholinergic
- Baclofen
- Other drugs
- Surgery
Botulinum toxin

• Potent neurotoxin: blocks release of acetylcholine at NMJ
• Cleaves presynaptic membrane proteins necessary for fusion of vesicles
• Produces temporary weakness until neurites regrow at NMJ
• Clinical use of types A, B and F
• Type A first treatment for cervical dystonia, blepharospasm, laryngeal dystonia
• Also for selected cases writer’s cramp and oromandibular dystonia
Drug therapy

• Critical to distinguish type of dystonia before starting therapy (e.g. Wilson’s, DRD, Myoclonus dystonia)

• Age of onset, duration of disease, extent of involvement, lifestyle an disability must be considered

• Drug therapy used more often for generalised rather than focal disease
  – Anticholinergics (trihexyphenidyl/artane)
  – Limited RCT evidence, one randomised double blind controlled trial of BT-A vs artane
  – Baclofen
  – Little data from trials
  – Other drugs (case reports/series only)
  – Tetrabenazine, clonazepam, primidone, valproate, carbamazepine, L-dopa, lithium, tetrahydrocannabinol
Surgery for dystonia: Functional neurosurgery

- Traditionally thalamotomy and pallidotomy in severe cases
- Deep brain stimulation has replaced radiofrequency lesioning
- Posteroventral Gpi stimulation used
- Stimulation needs to be continuous
- Indirect evidence for reversal of cortical plastic processes after GPi DBS
Prospective 3 year follow up for bilateral pallidal DBS in primary generalised dystonia.
Vidailhet et al Lancet Neurology 2007

• 22 patients studied over 3 years
• 17 completed 3 years – lead infection/fracture, lack of improvement
• Motor improvement at 1 year (51%) was maintained at 3 years (58%)
• Improvement in quality of life seen at 1 year, persisted at 3 years
Other indications for DBS

- Myoclonus dystonia syndrome
- Cervical Dystonia
- Oromandibular dystonia
- Status Dystonicus
- Secondary dystonias:
  - Tardive dystonia
  - X-linked dystonia parkinsonism
  - Battens disease
  - Pantothenate Kinase associated neurodegeneration
Pathogenetic mechanisms in Dystonia