Overview of Movement Disorders

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Objectives

- Learn the process of patient evaluation from a movement disorder perspective
- Identify characteristics and clinical presentation of various movement disorders
- Review diagnostic workup and first line treatment of movement disorders

What is a movement disorder?

- A group of neurologic conditions in which there is either:

1) a paucity or decrement of voluntary movement in the absence of weakness or spasticity (called akinesia, bradykinesia, **hypokinesia**)

2) an excess of movement, referred to as abnormal involuntary movements, dyskinesias, and **hyperkinesia**.

Hypokinesia vs Hyperkinesia

- **Hypokinesia:**
  - Parkinsonism
  - Drop attacks (Cataplexy)
  - Catatonia, psychomotor depression
  - Rigidity, Stiff muscles
  - Hypothyroid slowness
- **Hyperkinesia:**
  - Chorea, Athetosis, Ballism
  - Dystonia
  - Myoclonus
  - Tremor
  - Tics, RLS

Evaluation of a Movement Disorder

- Is the movement hypo or hyperkinesia?
- What is the nature of the invol. movement?
  - rhythmic vs. arrhythmic
  - Sustained vs. Non-sustained
  - Continuous vs. paroxysmal vs. induced
  - Sleep vs. Awake
  - Rest vs. Action
- What is the cause of the movements?
- Treatments

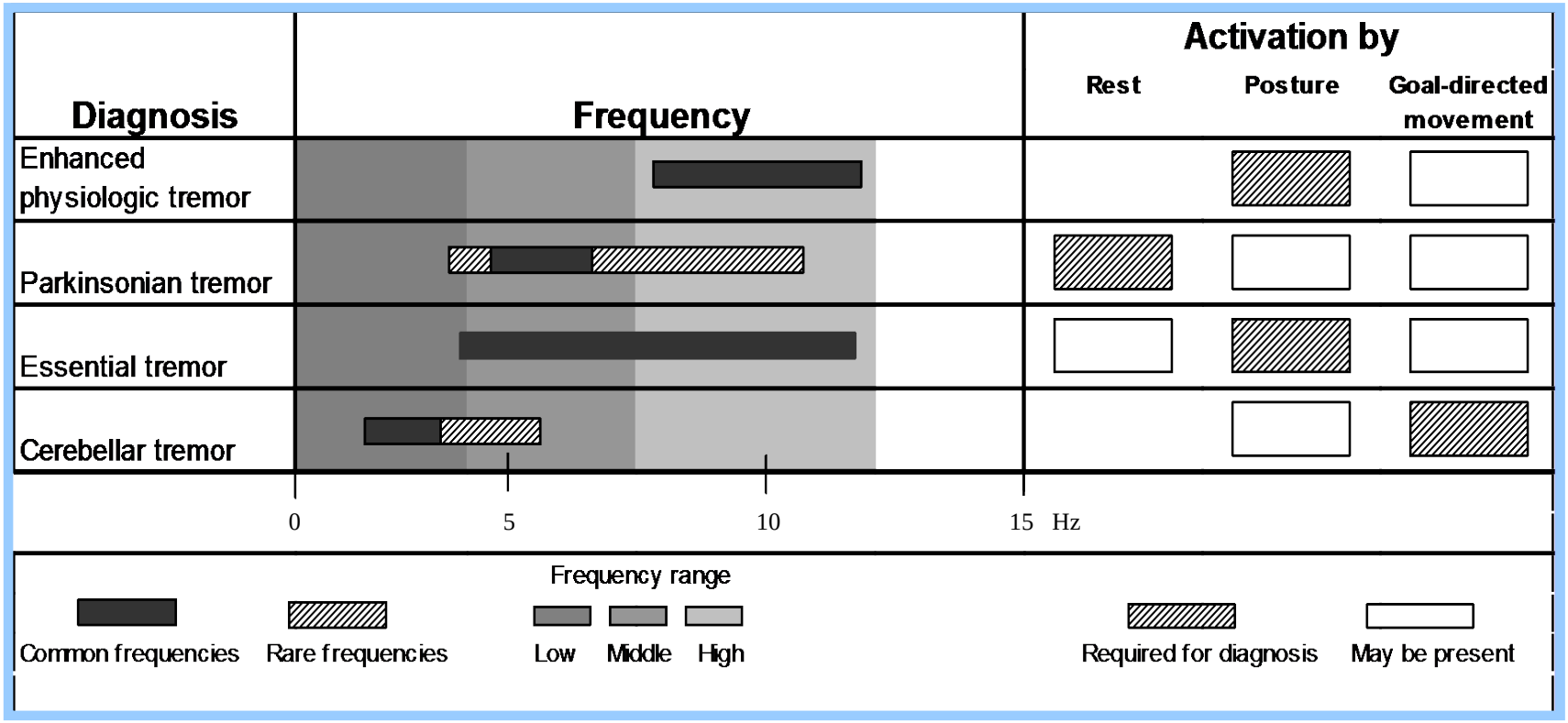
The “Shaky” Patient

- An involuntary, rhythmic, oscillatory movement of part or parts of the body
- Produced by alternating or synchronous contractions of antagonist muscles
- Most common involuntary movement disorder.

Classification Based on Clinical Phenomenology

- **Rest** — In absence of voluntary movement and with body part fully supported
- **Postural** — While voluntarily maintaining posture against gravity
- **Kinetic** — During voluntary movement
- **Task-Specific** — Kinetic tremor during specific, skilled movement
- **Orthostatic** — Tremor of lower extremities or trunk while standing in place

Classification of Tremor



Deuschl G, Bain P, Brin M, and an Ad Hoc Scientific Committee. Consensus statement of the Movement Disorder Society on Tremor. *Mov Disord.* 1998;13(suppl 3):2-23.

Essential Tremor

- Postural and/or kinetic tremor
- Frequency of 4.0 - 12.0 Hz
- Anatomic distribution (hands, head, voice, leg, jaw, face, trunk, tongue)
- Hands and forearms affected (70%)
- Typically bilateral
- Sporadic or inherited (60%)
- Alcohol responsive (74%)

Is it ET or PD?

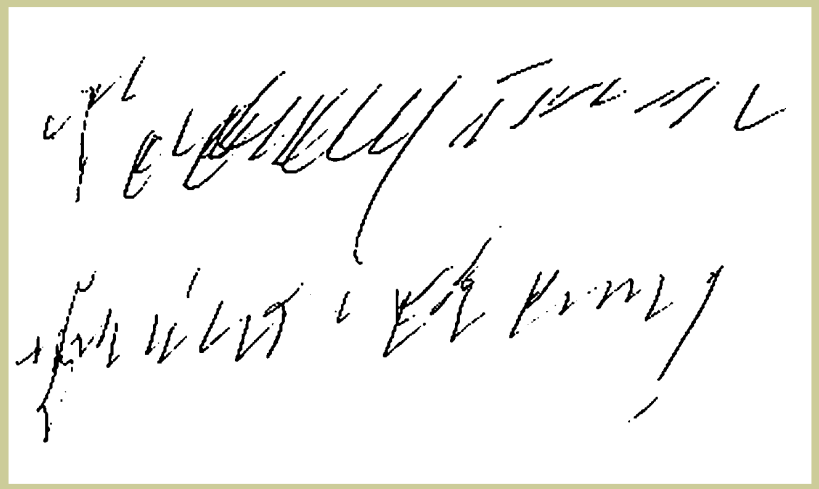
Essential Tremor

- **Action tremor**
- **More rapid frequency**
- **Not associated with slow movements, muscle rigidity and postural changes**
- **Often affects both sides**
- **Often familial**

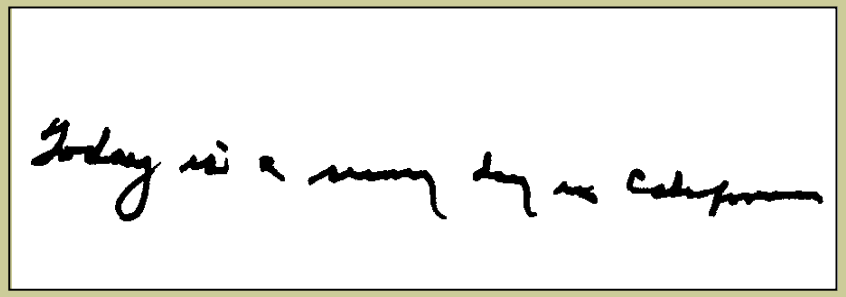
Parkinson's Disease

- **Resting tremor**
- **Slower frequency**
- **Associated with slowing, shuffling gait, rigidity, stooped posture, imbalance**
- **Usually worse on one side**
- **Rarely familial**

Handwriting Samples



Patient with ET



Patient with PD

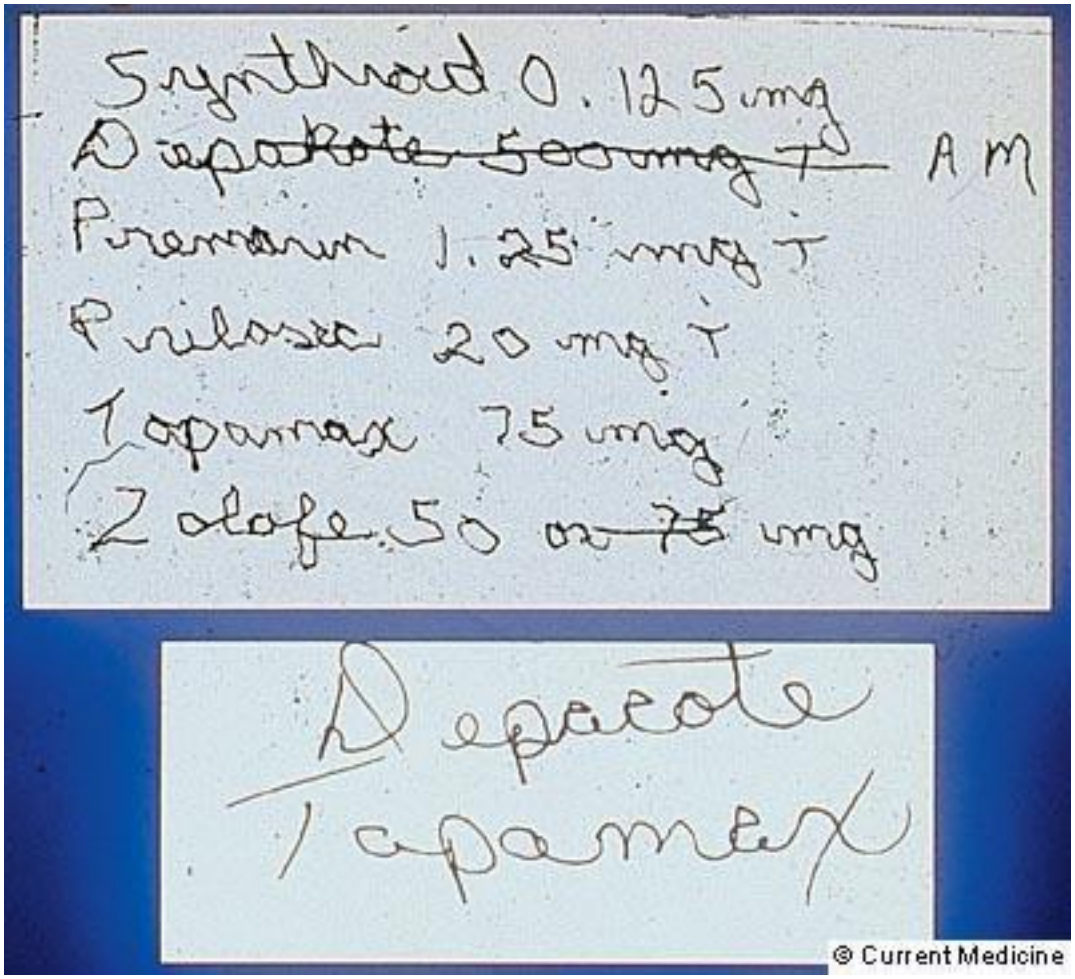
Differential Diagnosis

- Enhanced physiological tremor
- Essential Tremor
- Drug-induced tremor; tardive tremor
- Dystonic tremor
- Parkinson’s disease and parkinsonism
- Cerebellar/rubral tremor
- Task Specific Tremor (writing tremor)
- Tremor due to metabolic abnormalities (hyperthyroid, hypoglycemia, etc)
- Psychogenic Tremor

Drugs That May Induce Tremor

- Caffeine
- Cyclosporin
- Valproic acid
- Neuroleptics
- Antiemetics
- Reserpine
- Stimulants
- Metronidazole
- Prednisone
- Methylxanthines
- Lithium
- Bronchodilators
- Antidepressants
- Verapamil
- Atorvastatin
- Amiodarone
- Thyroxin
- Alcohol withdrawal
- Tocainamide

Drug-induced Tremor



Laboratory Investigation

- Thyroid function tests
- Ceruloplasmin and 24hr urine for copper
- CT or MRI brain scan

- Testing needed in patients not consistent with idiopathic PD or ET

Pharmacological Therapy

1) Propranolol - 240 to 320 mg/d optimal dose range

- Approximately 40% to 50% of patients benefit
- Reduction in amplitude by 50% to 60%; no effect on frequency
- Most effective against hand; some effect on head and voice.

2) **Primidone** – 50 to 750 mg/d optimal dose range

- Single dose can reduce amplitude of arm tremor by 60%
- Complete suppression of tremor can be achieved
- Response of head and voice tremor less consistent

Second line Meds: Topamax, Zonegran, Gabapentin, Klonopin, Remeron, and Lyrica.

Koller WC, et al. *Neurology*. 2000;54(suppl 4):S30-S38.

The “Dancing” patient

- Chorea – involuntary, continuous, abrupt, rapid, brief, un-sustained, and irregular movement that flow randomly from body parts
- Athetosis – a slow form of chorea the consists of writhing movements.
- Ballism – Forceful, flinging, high-amplitude coarse form of chorea

Chorea - Clinical Features

- Clinical Features:

- Movements can be partially or temporarily suppressed
- Motor Impersistence – is the inability to maintain voluntary contraction: milkmaid grip, tongue protrusion
- Chorea may be the manifestation of a neurodegenerative disorder (Huntington's disease) or as a complication of systemic, toxic, disorder

Hemiballism

- Large amplitude proximal chorea
- Relates to structural lesion in contralateral hemisphere
  - Subthalamic nucleus
  - Interconnections between striatum, subthalamic nucleus, thalamus, etc.
- Primary causes
  - Elderly—vascular, nonketotic hyperglycemia
  - Young—infectious, inflammatory

Differential Diagnosis

- **No Family History (Sporadic Cause)**:

  Essential (senile) Chorea
  Vascular: Stroke, Vasculitis, etc
  Infectious: Sydenham's Chorea, lyme, AIDS, CJD
  Polycythemia Vera
  Autoimmune: Lupus, Anti-phosholipid Syndrome
  Metabolic: Hyperthyroidism, Non-ketotic Hyperglycemia,Hyponatremia, Pregnancy
  Paraneoplastic
  Tardive Dyskinesia
  Drug-induced

Chorea--Differential Diagnosis Drug-induced

- Oral contraceptives
- Anticonvulsants
- Anti-nausea – reglan, compazine, etc
- Thyroid replacement
- Cocaine
- Amphetamines
- Tricyclic antidepressants
- Neuroleptics
  - Withdrawal-emergent
  - Tardive

Differential Diagnosis

- **Positive Family History:**

  Autosomal dominant
  - Huntington's disease
  - HD-like-illnesses (1,2,4)
  - Spinocerebellar ataxias (1,2,3,17,DRPLA)
  - Fahr's syndrome
  - Neuroferritinopathy
  - Benign Hereditary Chorea

  Autosomal recessive
  - HD-like-illnesses (3)
  - Neuroacanthocytosis
  - Wilson's disease
  - Neuronal degeneration with brain iron accumulation type I
  - Pantothenate kinase associated neurodegeneration

  X Linked Recessive – Mcleod syndrome

Evaluation of Chorea

- History, physical examination
  - Detailed family history
  - Detailed medication history
- Routine blood work:

  Urine tox, TFTS, CMP, ESR, ANA, CBC, Pregnancy, ASO titer/anti-dnase AB, antiphospholipid AB, copper/ceruloplasmin
- MRI for acute onset, hemichorea
- Genetic studies: HD, SCA…

Treatment of Chorea

- Treat underlying Cause
- Dopamine receptor blockade
  - Typical neuroleptics—*caution!*
  - “Atypical” neuroleptics
- Presynaptic dopamine depletion
  - Reserpine (no longer available in the US)
  - Tetrabenazine (Xenazine)
    - 25-100 mg/day
- Glutamate antagonism
  - Amantadine
- GABA-ergic
  - Valproic acid

The “Jerky” Patient

Myoclonus:

Sudden, brief, shock-like involuntary movements caused by muscular contraction or inhibition, originating either in the central or peripheral nervous system

Positive myoclonus – contraction of muscle

Negative myoclonus – brief loss of agonist muscle tone (asterixis)

Clinical Classification

Anatomic:

- **Focal:** restricted to one body part
- **Segmental:** Involve adjacent part of body and is typically due to spinal cord damage
- **Multifocal –** 2 or more non-adjacent areas
- **Generalized –** Synchronous jerks of one of more major muscle groups

Provocative Factors:

- Spontaneous

- Stimulus Sensitive (Reflex) auditory, verbal

- Action

Etiologic Classification

- **Physiologic** - Hypnagonic, hiccups, benign infantile myoclonus
- **Essential** - Idiopathic, usually with positive family history (AD) and is ETOH responsive. Can occur with dystonia (epsilon-sarcoglycan gene – DYT11)
- **Epileptic** - epilepsia partialis continua, myoclonic absence, infantile spasms, juvenile myoclonic epilepsy
- **Secondary –** metabolic, toxin, drug induced, celiac, neurodegenerative disease, encephalopathy

Diagnostic Work-up

- Careful review of all medications and supplements
- Alcohol intake and illicit substance use history
- Detailed family history of neurologic disturbances
- CMP, ammonia, LFT, BUN/CR, TFT, celiac panel
- EEG in patients with a history of seizures or cardiac arrest
- Pediatric cases: search for infectious or paraneoplastic cause (neuroblastoma – opsoclonus-myoclonus)
- MRI in most patients (brain or spinal cord)
- EMG - Cortical/Subcortical Myoclonus is < 100 ms

  Spinal > 200 ms Psychogenic latency > 100 ms

Drugs That May Induce Myoclonus

- Lithium
- Opiates
- SSRI and TCA antidepressants
- Anticonvulsants – tegretol, dilantin, lamictal, gabapentin, vigabatrin
- Dopamine agonist and Levodopa
- Anti-psychiotics (Tardive myoclonus)
- Anesthetic agents like propofol and fentanyl

Treatment guidelines

- Treat Underlying cause
- Most myoclonus Rx is symptomatic
- Unlike epilepsy, most patients with myoclonus require treatment with more than one drug

Anti-Myoclonic Agents

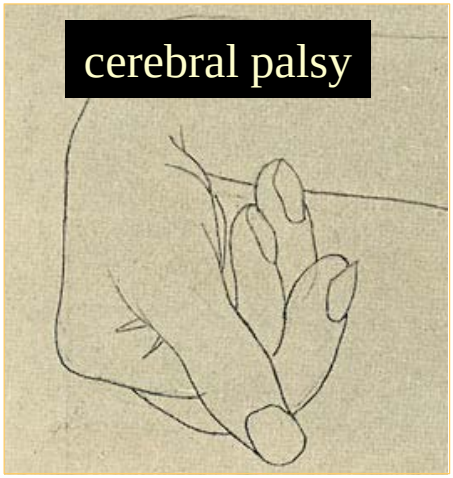
OLD	NEW
VPA	Levetiracetam
Clonazepam	Zonismide
Phenobarbital	Sodium Oxybate
Acetazolamide	(Xyrem)

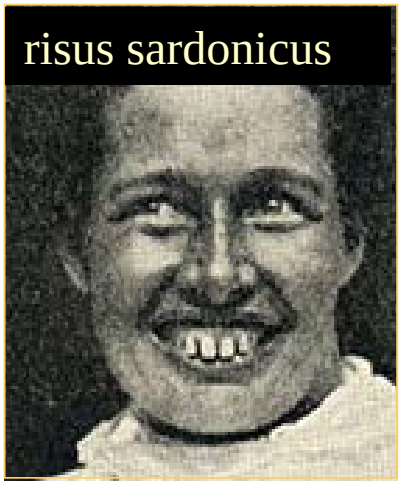
The “Twisted” Patient

Dystonia is a syndrome of **sustained** muscle contractions, frequently causing **twisting** and repetitive movements or abnormal **postures**

The movements are of a long duration and both agonist/antagonist muscles are contracting resulting in twisting movements

Classic examples of the dystonic phenotype: note the sustained postures





Wilson
1912

Julius
Ceasar

Unique Features of Dystonia

Task-specificity: involuntary movements by specific tasks
Geste antagoniste: a sensory trick that improves the dystonic phenotype
State function: variation in severity of dystonia with specific actions (walking backwards but not forwards, speaking but not eating).

Distribution of dystonia

- Focal:

  - Task specific: writer's cramp, musician

  - Blepharospasm

  - Meige syndrome

  - Jaw: opening/closing

  - Cervical torticollis

  - Arm or Leg

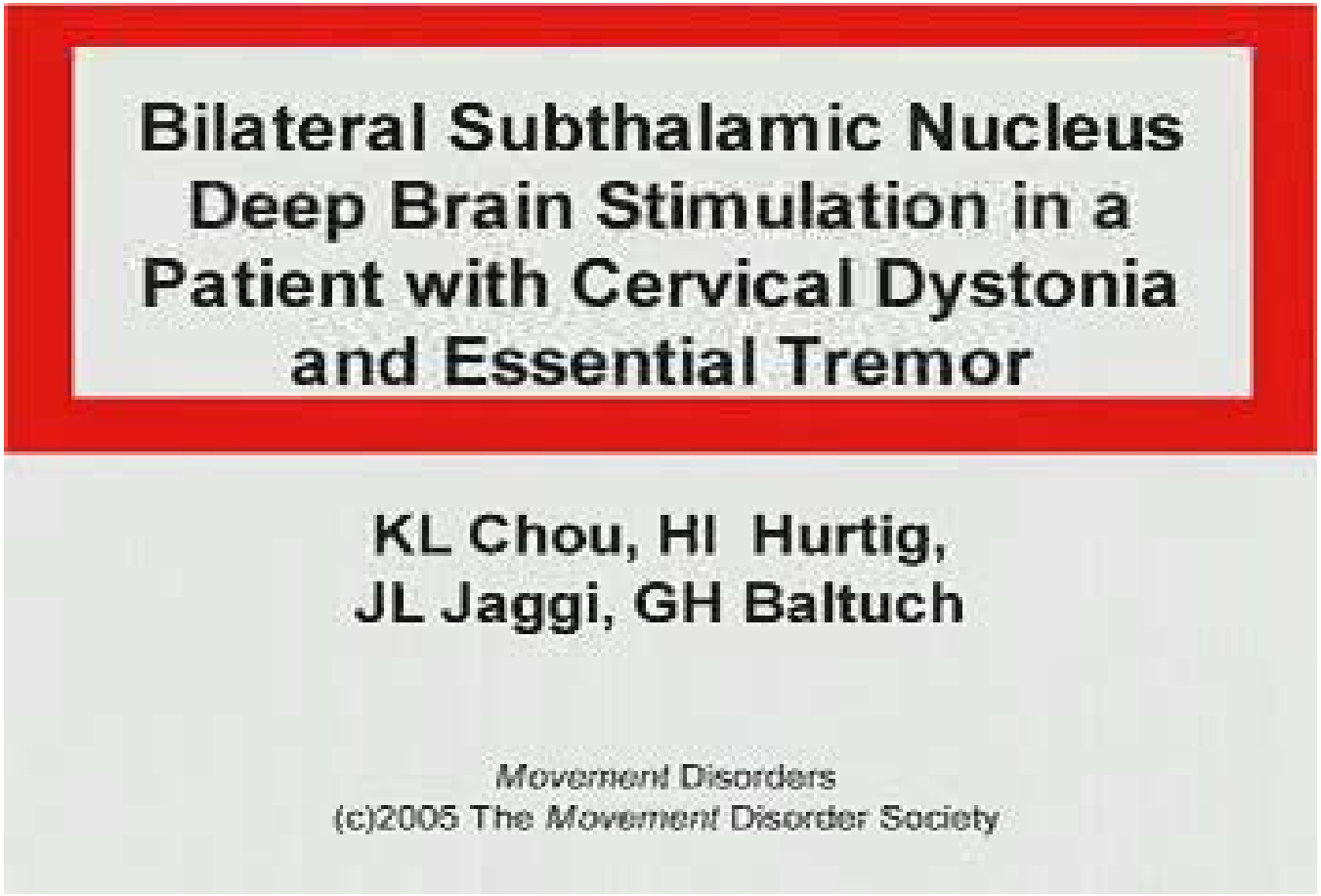
- Segmental – adjacent body part

Hemidystonia – unilateral

Generalized

Multifocal – non-adjacent body parts

Cervical Dystonia



Classification of dystonia by etiology

- **Primary dystonia** (genetic): dystonia is present in isolation with no other neurologic deficits. Rarely begin after the age of 26.
- **Dystonia-plus syndromes**: dystonia is accompanied by one other neurologic abnormality (typically parkinsonism - DYT-5 or myoclonus - DYT-11)
- **Secondary dystonia**: due to an external factor, stroke, cerebral palsy, toxin or drug (tardive).
- **Heredodegenerative dystonia**: dystonia occurs as a feature of a generalized, inherited neurologic disturbance.

Evaluation of Dystonia

Primary dystonia: clinical, genetic (DYT 1)

Dystonia-plus: clinical diagnosis, confirmed by response to treatment. Genetic testing

Secondary dystonia: MRI of brain

Heredodegenerative dystonia: MRI of brain, ceruloplasmin, slit-lamp exam, lysosomal screen, peripheral blood smear, NCV, CK,

Psychogenic: Psychiatric evaluation, exam under anesthesia.

Primary Dystonia (DYT)

DYT 1—9q34, Oppenheim's dystonia
DYT 2—AR, Spanish gypsies
DYT 3—Xq13.1, X-linked dystonia-parkinsonism
DYT 4—whispering dysphonia
DYT 5—14q22.1, Dopa-responsive dystonia
DYT 6—8p21, Mennonite
DYT 7—18p, familial torticollis
DYT 8—2q33, paroxysmal non-kinesigenic dyskinesia
DYT 9—1p, paroxysmal dyskinesia with spasticity
DYT 10—16p11.1, paroxysmal kinesigenic dyskinesia
DYT 11—7q21, Myoclonus-dystonia
DYT 12—19q, rapid-onset dystonia parkinsonism
DYT 13—1p36, cranial-cervical-brachial dystonia
DYT 14—dopa-responsive dystonia
DYT 15—18p, myoclonus-dystonia

Primary Dystonia—DYT-1

DYT-1: Autosomal dominant

- Clinical penetrance of only 30-40%

- All cases are due to single GAG deletion in torsin A on chromosome 9q34.1

- Onset is typically in the first decade, often affecting a limb (arm or leg). The risk of spread of dystonia is related to age (higher risk in younger patients), and site of onset (higher risk in leg).

Treatment of dystonia: guidelines

- Treat the underlying neurologic disorder.

- Medical therapy: All children should be treated with levodopa (DYT-5)

ABC: Artane, Baclofen, Clonazepam

Botulinum toxin injection: the treatment of choice for focal dystonia.

- Deep brain stimulation: for severe, medication refractory generalized dystonia; use in focal dystonia is experimental.

The “Psychogenic” Patient

- Abrupt onset
- Inconsistent movements
- Incongruous movements and postures
- Additional abnormal movements
- Spontaneous remission
- Distraction
- Paroxysmal
- Onset as a fixed posture
- Side-to-side mouth movements

THE END

Dopa-responsive dystonia - DYT-5

DYT5 - Autosomal dominant

- Onset is usually in the first decade of life, typically affecting the foot, often with diurnal variation (worse later in the day, better after sleep). Improves with walking backwards.
- Dramatic response to low-dose levodopa without the development of motor fluctuations or dyskinesias.
- Most cases due to a mututation in the GTP cyclohydrolase I gene.

Pathophysiology of Myoclonus

- **Cortical**:

  - Spontaneous/stimulus induced Multifocal myoclonus

  - Focal cortical lesion (tumors, angioma, encephalitis)

  - Epilepsy – PME, MERRF, Epilepsia partialis continua

- **Subcortical**:

  - Stimulus induced Generalized myoclonus

  -Typical secondary to hypoxia (Lance-Adams Syndrome) Metabolic (asterixis), Parkinsonism, or CJD

  - **Brainstem:** 1) Exaggerated Startle Syndrome (hypereplexia)
  2) Brainstem Reticular Myoclonus – Epileptic RF
  3) Palatal myoclonus – rhythmic movement of the palate that persists during sleep

Pathophysiology of Myoclonus

- **Spinal Cord:**

  - **Spinal Segmental** – Adjacent segments of the cervical or thoracic cord, is typically rhythmic, and may be stimulus-sensitive.

  - **Propiospinal** – Generalized axial jerks stimulus sensitive due to thoracic lesion

  - **Peripheral** – Arrythmic, spontaneous jerks due to lesion of peripheral nerve, plexus, root

Heredodegenerative dystonia---the needle in the haystack

Metal and Mineral Metabolism

Wilson Disease

Neurodegeneration with brain iron accumulation Type I (formerly Hallervorden-Spatz disease)

Neuroferritinopathy

Idiopathic basal ganglia calcification (Fahr disease)

Lysosomal Storage Disorders

Niemann-Pick disease type C

GM1 Gangliosidosis

GM2 Gangliosidosis

Metachromatic Leukodystrophy

Krabbe Disease

Pelizaeus-Merzbacher Disease

Neuronal ceroid lipofuscinosis (Batten disease)

Fucosidosis

Inborn errors of Metabolism

Lesch-Nyhan Syndrome

Aromatic amino acid decarboxylase deficiency

Triosephosphate Isomerase Deficiency

Guanidinoacetate Methyltranferase Deficiency

Molybdenum cofactor deficiency

Glucose Transport Defects

Amino and Organic Acidurias

Glutaric Acidemia type I

Homocystinuria

Priopionic acidemia

Methlymalonic Aciduria

4-hydroxybutyric aciduria

3-methylglutaconic aciduria

2-oxoglutaric aciduria

Hartnup's Disease

Mitochondrial disorders

Leigh Disease

Leber's Hereditary Optic Neuropathy

Mohr-Tranenberg syndrome- dystonia, deafness

Trinucleotide repeat disorders

Huntington's disease

Spinocerebellar ataxia-3 (Machado-Joseph disease) and other SCAs

Parkinsonian syndromes

Parkinson's disease

Progressive supranuclear palsy

Multiple system atrophy

Corticobasal ganglionic degeneration

Juvenile-onset parkinsonism

X-linked dystonia-parkinsonism (Lubag)

Rapid-onset dystonia-parkinsonism

Other degenerative processes

Ataxia-telangiectasia

Chorea-acanthocytosis

Rett syndrome

Infantile Bilateral Striatal Necrosis

Neuronal intranuclear inclusion disease

Ataxia with vitamin E deficiency

Progressive pallidal degeneration

Sjogren-Larsson Syndrome

Ataxia-Amyotrophy-Mental Retardation-Dystonia Syndrome