Chorea: Causes and Treatment

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CNSF: Movement Disorders session
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Objectives

• To understand causes of chorea and diagnostic work-up

• Review options for treating chorea
Disclosures

• Funding for basic research on mechanism of action of Pridopidine, from TEVA Pharmaceuticals, LTD
Distinguishing chorea from other hyperkinetic movement disorders

Involuntary movement:

- *Tremor* - rhythmic, intermittent
- *Myoclonus* – Rapid, shock-like jerks of body part or muscles
- *Dystonia* – Sustained muscle contraction (twisting, squeezing, abnormal postures)
- *Chorea-athetosis* – irregular and unpredictable jerks that are brief, shifts from one part of body to another, fidgety and/or writhing, dance-like
Recognizing chorea
Basal Ganglia: Direct vs Indirect pathways

D1 – Substance P, dynorphin
D2 – Enkephalin
Basal Ganglia: Effect of dopamine

Promotes chorea

DA from SNc -

↑ D1 MSN

↑ D1 MSN Direct pathway

GPM SNr THAL CTX

↓ D2 MSN

↓ D2 MSN Indirect pathway

GP STN SNr THAL CTX
Chorea: Direct > Indirect pathways

Promotes chorea
Chorea – imbalance of direct and indirect pathways from striatal neurons

• Huntington’s disease: selective loss of D2 (indirect “Stop” pathway) in early/mid stage → chorea

• Parkinson’s disease treated with dopamine agonists or L-DOPA (“on-state”): results in dopamine peaks that shift balance – increased D1, direct pathway and reduced D2, indirect pathway → chorea

• Dopamine agonists, anticholinergic drugs (ACh inhibits D1, direct pathway)
Other causes of chorea (1)

- **Autoimmune/inflammation:** Multiple sclerosis, Systemic Lupus Erythematosis, Sjogren’s, Anti-phospholipid antibodies, anti-NMDAR, HIV or other viral infection, paraneoplastic syndrome

- **Endocrine:** Pregnancy, post-partum, hyperthyroid, hyper- or hypo-parathyroid

- **Hematologic:** Polycythemia (iron deposition in BG), neuroacanthocytosis (autosomal recessive or X-linked with acanthocytic RBCs and BG degeneration)

- **Metabolic:** Liver (hepatocerebral degeneration), hyperglycemia, celiac disease

- **Degenerative:** BG ischemia or calcification

- **Mitochondrial disorders**
Other causes of chorea (2)

• **Inherited:** Huntington’s disease (Autosomal dominant - AD) is most common; Wilson’s disease (Autosomal recessive - AR); SCA-1,2,3,17 (AD); Friederich’s ataxia (AR); ataxia-telangiectasia (AR); neuro-ferritinopathy (AR)

• **Drugs:**
  • Levo-DOPA
  • Anti-convulsants – Dilantin, GABApentin, Lamotrigine
  • Contraceptives and other sources of estrogen, progesterone
  • Psychiatric meds – Li+, chronic antipsychotics (tardive dyskinesia)
Diagnostic work-up

- Serum ferritin, ceruloplasmin, liver enzymes
- TSH, parathyroid hormone, serum glucose
- RBC count and smear for acanthocytes
- ANCA, Sjogren’s screen, anti-phospholipid antibody, anti-NMDAR antibodies
- Consider paraneoplastic screen
- **Genetic screening** – especially HD gene mutation, and consider SCA’s, Wilson’s
Chorea – Treatment options

• Suppress dopamine drive with anti-dopaminergics, e.g. antipsychotics (olanzapine, risperidone, haloperidol, etc)
  • Can get hyperkinetic movement disorder – tardive dyskinesia – as a result of chronic antipsychotic; however, can potentially avoid by keeping doses low
  • Olanzapine – sedating, given mainly at bedtime; weight gain is side effect (good for patients with HD)
  • Risperidone – as dose increased has extrapyramidal side effects, especially dysphagia and retropulsion
Chorea – Treatment options (2)

• Suppress dopamine drive by depleting dopamine from vesicular stores in nerve terminals (Tetrabenazine)
  • First anti-choreic approved for treatment in Huntington disease (HD)
  
  • Psych side effects include depression, anxiety, akathisia
  • Keep dose as low as possible, and <75mg/day in patients with HD to avoid psychiatric side effects
  • Other side effects – sedation, dysphagia
Chorea – new treatment in HD

• Newly approved drug for treatment of chorea in HD: **Deutetrabenazine**
  • Prolongs activity of tetrabenazine by slowing its metabolism
  • Requires smaller doses to achieve same anti-choreic effect
  • Reduced side effects because of lower dose, less intense peaks/troughs

*Huntington Study Group, Frank S, Testa CM et al. (2016) Effect of Deutetrabenazine on Chorea Among Patients with Huntington Disease: A Randomized Clinical Trial. JAMA 316:40-50.*
Chorea – other treatments

• **Aripiprazole** - Partial dopamine receptor agonist
  - Binds dopamine receptor and can activate it, but to a lesser degree than full agonists like dopamine; therefore, if dopamine levels too high, it acts to limit receptor activation and if too low, it can partially stimulate receptor

• **Antiepileptics** – valproate, carbamazepine

• **Clonazepam** – can cause some sedation, ataxia so give mainly at night to suppress movement and thereby help with sleep
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Centre for Huntington Disease at UBC

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QUESTIONS?

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