CHOREA

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INTRODUCTION

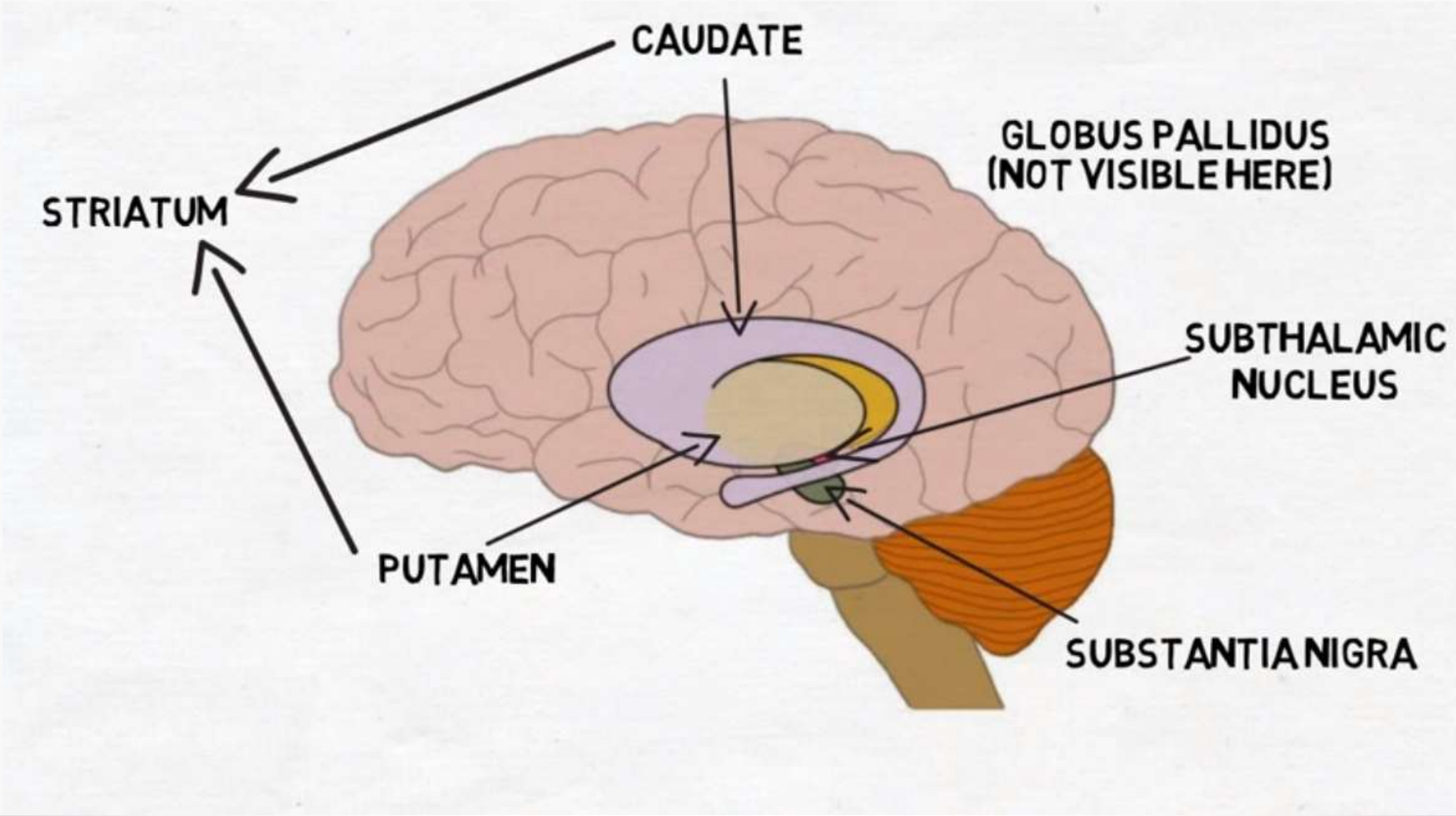
- "chorea" meaning "dance."
- hyperkinetic movement disorder characterized by involuntary brief, random, and irregular contractions
- Seen in hereditary neurodegenerative diseases, following structural damage to deep brain structures, or associated with autoimmune disorders, metabolic derangement, or certain drugs and hormones
- When due to acquired conditions chorea may be reversed. There is usually no specific therapy for hereditary causes
- Symptomatic treatment can reduce abnormal movements regardless of the cause

DEFINITION

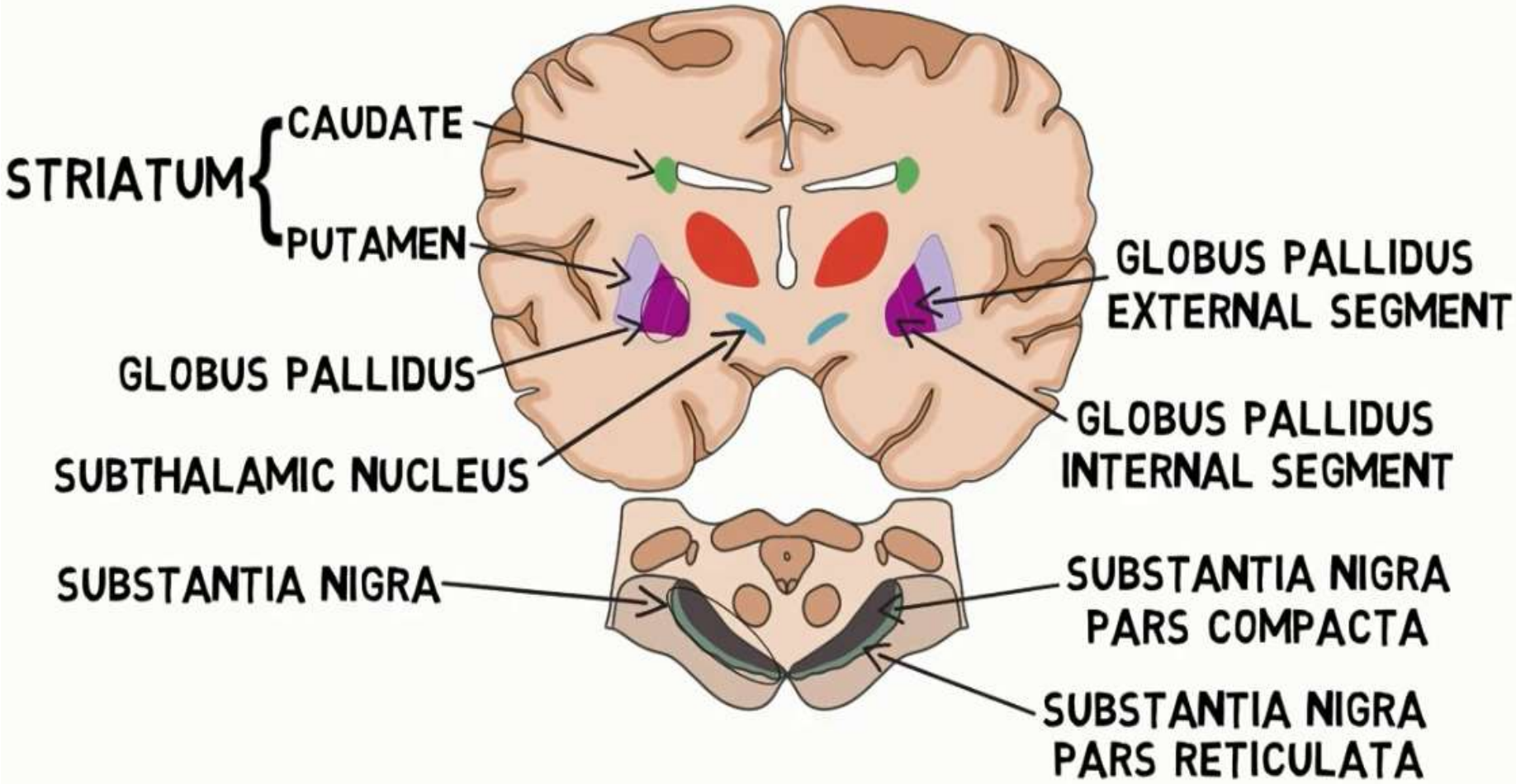
- Chorea, athetosis, and ballism often coexist in the same patient and felt to be of the same spectrum
  - Chorea:
    - hyperkinetic movement disorder characterized by rapid, unpredictable contractions
      - Unpredictability distinguishes from tremor and dystonia.
    - affects mostly distal limbs, as well as face and trunk.
    - Movements involuntary with variable speed, timing, and direction.
  - Athetosis:
    - slower, writhing movements with a sinuous quality.
      - "choreoathetosis":choreic movements coexistent with athetosis.
  - Ballism:
    - Proximal, large amplitude, involuntary movements, with a flinging or kicking character.
    - Most often unilateral (hemiballism)
    - Present at rest, but more pronounced with action

ETIOLOGY

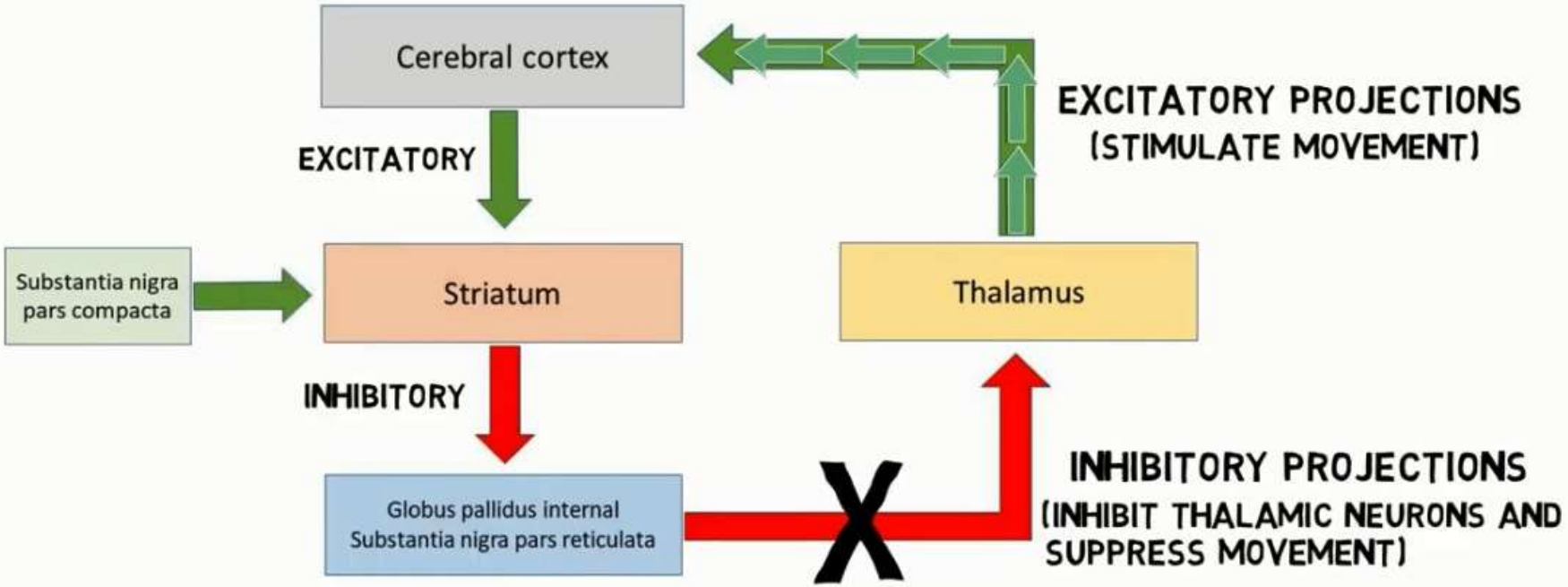
- structures involved in the pathophysiology of chorea: caudate nucleus, putamen, subthalamic nucleus, thalamus, and their interconnecting pathways
  - Chorea results from damage or dysfunction of these structures that causes an imbalance between indirect and direct pathways in the basal ganglia circuitry, leading to excessive dopaminergic activity.
    - Disruption of the indirect pathway with loss of inhibition to the pallidum allows hyperkinetic movements to occur
    - disruption of basal ganglia circuitry may be due to:
      - structural damage, selective neuronal degeneration, neurotransmitter receptor blockade, metabolic derangements, or autoimmune conditions


CAUDATE
GLOBUS PALLIDUS
(NOT VISIBLE HERE)
STRIATUM
SUBTHALAMIC
NUCLEUS
PUTAMEN
SUBSTANTIA NIGRA

BASAL GANGLIA



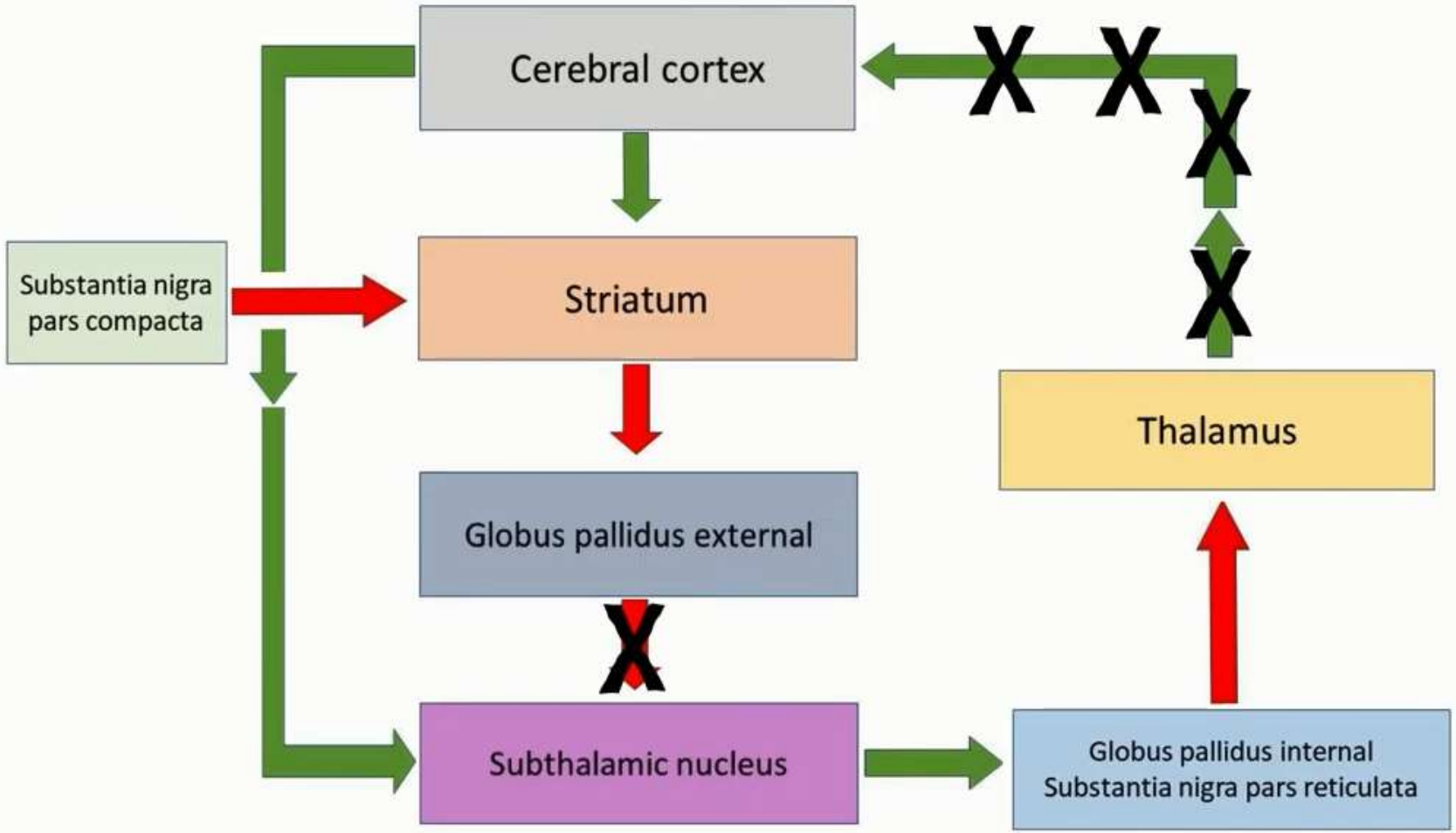
DIRECT PATHWAY
(SIMPLIFIED MODEL)



INDIRECT PATHWAY

(SIMPLIFIED MODEL)

GREEN ARROWS REPRESENT EXCITATORY CONNECTIONS, RED ARROWS REPRESENT INHIBITORY CONNECTIONS



EPIDEMIOLOGY

- Huntington disease (HD) is the most frequent cause of hereditary chorea, with a worldwide prevalence rate of approximately 3 per 100,000
- Most common causes of acquired chorea
  - Adults:
    - Vascular
    - Drug-induced (levodopa-induced dyskinesia)
    - AIDS
  - Children:
    - Rheumatic fever (Sydenham chorea)

CLASSIFICATION

- Primary (hereditary) vs. Secondary (acquired)
  - Insidious vs. Acute/Subacute
  - Symmetrical/Bilateral vs Asymmetrical/Unilateral
    - In any case of unilateral chorea, a focal lesion should be sought.
- Age of Onset

CLINICAL FEATURES

- Chorea usually affects the distal limbs and face, but may also interfere with respiration and phonation, resulting in slurred speech or involuntary vocalizations
- continuous flow of movements may appear semi-purposeful and difficult to distinguish from restless or fidgety behavior
  - patients may mask the chorea by incorporating choreic movements into voluntary movements (parakinesia)
  - Patients are often unaware of their abnormal movements

HEREDITARY CAUSES OF CHOREA

Autosomal dominant

- Huntington disease
  - CAG expansion of HTT on chr. 4p
  - Anticipation
- C9ORF72 repeat expansions
- Huntington disease-like syndromes
- Benign hereditary chorea
- Dentatorubral pallidoluysian atrophy
- Spinocerebellar ataxias
- Neuroferritinopathy
- ADCY5 and PDE10A mutations

Autosomal recessive

- Chorea-acanthocytosis
- Wilson disease
  - Suspect in patient under 40 yo with movement disorder
  - Rare but treatable cause of chorea
- Pantothenate kinase-associated neurodegeneration
- Ataxia-telangiectasia
- Ataxia with oculomotor apraxia

X-linked

- McLeod syndrome
- Lesch-Nyhan syndrome
  - HGPRT deficiency
  - Pediatric onset
  - Dystonia more common than chorea

ACQUIRED CAUSES OF CHOREA

- Vascular
  - MC acquired cause
  - acute ischemic or hemorrhagic stroke
  - low-grade ischemic changes in the basal ganglia without obvious infarction
  - lesion of the subthalamic nucleus is found in only a minority of cases
  - Other reported localizations include the caudate nucleus, putamen, thalamus, globus pallidus, corona radiata, subcortical white matter, and cortex
  - most stroke lesions causing hemichorea/hemiballism involve a common functional network connected to the posterolateral putamen

- Autoimmune or inflammatory disorders
  - Sydenham chorea
  - Paraneoplastic chorea
  - Other immune-mediated choreas
    - Uncommon manifestation of SLE
      - Associated with antiphospholipid Abs
      - Precipitated by pregnancy/OCPs
- Metabolic and endocrine disorders
  - Nonketotic hyperglycemia
- Chorea gravidarum
- Other metabolic or endocrine disturbances
- Infectious diseases
  - HIV
- Toxin exposure
- Structural lesion in basal ganglia
- Senile chorea
- Edentulous dyskinesia

- Drug-induced chorea
  - Parkinson's treatment
    - Levodopa
  - Antipsychotics
    - 'tardive dyskinesia'
  - Drugs that can cause chorea
    - Dopaminergic medication
      - COMT inhibitors with levodopa
      - Dopamine agonists
      - Levodopa
    - Dopamine blocking agents
      - Amantadine
      - Anticholinergics
      - Atypical neuroleptics
      - Typical neuroleptics
    - Dopamine depleting agents
      - Reserpine
      - Tetrabenazine
    - Anticonvulsants
      - Carbamazepine
      - Gabapentin
      - Lamotrigine
      - Phenytoin
      - Valproic acid
    - Calcium channel blockers
      - Cinnarizine
      - Flunarizine
      - Verapamil
    - Central nervous system stimulants
      - Amphetamines
      - Cocaine
      - Cyproheptadine
      - Methylphenidate
    - Others
      - Aminophylline and theophylline
      - H1 & H2 blockers)
      - Baclofen
      - Benzodiazepines
      - Cimetidine
      - Cyclosporine
      - Digoxin
      - Estrogens and oral contraceptives
      - Glucocorticoids
      - Isoniazid
      - Levofloxacin
      - Lithium
      - Opioids
      - SSRIs
      - Sympathomimetics
      - Tricyclic antidepressants

EVALUATION OF CHOREA

- History should include:
  - Age of onset
  - Time course (acute or insidious)
  - PMH
  - FH
  - Recent group A streptococcus infection
  - Drug exposure
- Chronic and progressive chorea → typical of neurodegenerative diseases
- Static chorea → structural or toxic injuries to basal ganglia or in benign hereditary chorea
- Subacute or acute chorea → autoimmune, metabolic, vascular, infectious, or toxic causes.

- Neurologic examination is also crucial and must include distribution of chorea and associated features:

  - Hemichorea
    - Likely a structural lesion.
    - Also possible with:
      - autoimmune chorea
      - metabolic choreas
      - chorea gravidarum.
  - Chorea + Ataxia:
    - spinocerebellar ataxia (SCA) types 1, 2, 3, or 17
    - dentatorubral pallidoluysian atrophy (DRPLA),
    - ataxia-telangiectasia
    - ataxia with oculomotor apraxia types 1 (AOA1) or 2 (AOA2)
  - Chorea + Dementia:
    - Huntington disease (HD)
    - Huntington disease-like (HDL) syndromes
    - SCA17
    - DRPLA
    - chorea-acanthocytosis.
  - Chorea + peripheral neuropathy:
    - chorea-acanthocytosis
    - McLeod syndrome
    - SCA
    - ataxia-telangiectasia
    - AOA1 or AOA2

- Work up for secondary cause:
  - Complete blood count
  - Serum glucose and electrolytes
  - Serum calcium, magnesium, vitamin B12, and parathyroid levels
  - Renal, liver, and thyroid function tests
  - Pregnancy test

- Blood smear may show acanthocytes:
  - Chorea-Acanthocytosis, McLeod syndrome, HDL2, and pantothenate kinase-associated neurodegeneration (PKAN).
- In suspected Sydenham chorea (SC);
  - Major/minor symptoms and signs of rheumatic fever, including evaluation for carditis;
    - antideoxyribonuclease B titers
    - antistreptolysin O titers
- Screening for possible autoimmune chorea:
  - Antinuclear antibodies and antiphospholipid antibodies
    - paraneoplastic evaluation would add anti-CRMP5/CV2 and anti-Hu antibodies.
- Screening for Wilson disease:
  - Serum ceruloplasmin and 24-hour urine copper
    - movement disorder under the age of 40 years
      - especially with a positive family history of neuropsychiatric disorders or liver disease.
- Workup for infectious causes of chorea:
  - Directed by the clinical setting and degree of suspicion for particular infections
  - HIV testing
  - Lumbar puncture for cerebrospinal fluid examination including VDRL
  - Lyme serologies
  - Toxoplasmosis titers (in immunosuppressed patients)

- Neuroimaging with brain MRI (preferred) or CT:
  - rule out structural lesion in patients with focal or unilateral choreas
    - may also reveal evidence of hereditary, immunologic, or metabolic choreas
      - caudate and frontal atrophy in HD
      - cerebellar atrophy in SCA
      - basal ganglia anomalies in neuroferritinopathy, chorea-acanthocytosis, Wilson disease, PKAN, liver dysfunction, or hyperglycemia.

- Genetic testing for hereditary choreas
  - confirmation of the diagnosis and genetic counseling

MANAGEMENT OF CHOREA

- Treatment is directed towards the underlying etiology, VMAT2Is (first-line), and rarely, surgical intervention.

THANK YOU