

CHOREA AND DYSTONIA

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INTRODUCTION

The key to successful differential diagnosis and treatment of patients with movement disorders is successful identification of the phenomenology of the abnormal movements.

“**Chorea**” is defined as a quick, irregular, jerky, purposeless movement that moves randomly from one body part to another in an unpredictable manner. It may be associated with other movements such as dystonia, ballism, or athetosis. It is differentiated from other movement disorders by its non-patterned, non-rhythmic, and constantly changing characteristics.

“**Dystonia**” is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures or both. The movements are typically patterned, twisting and may be tremulous. Dystonia is often imitated or worsened by voluntary action and associated with *overflow muscle activation*. The hallmarks of dystonia include the patterned and predictable nature of symptoms. Other unique and differentiating features can include the presence of *mirror dystonia*, in which a unilateral posture or movement that is the same or similar in character to a dystonic feature, when contralateral movements are performed. A *sensory trick* (“geste antagoniste”) can often be elicited, in which a voluntary action that specifically corrects the abnormal posture or relieves the movement is seen.

CHOREA

a. Phenomenology

Chorea is typically generalized in distribution, though in some conditions, symptoms may be localized to one region (e.g., both legs, as in levodopa-induced dyskinesia, or the hemibody, as in vascular causes). The onset of chorea can be acute, subacute, or chronically progressive, and understanding the presentation and course are important factors in considering the differential diagnosis. Some forms are relatively static, while others are episodic. In progressive conditions, chorea generally begins distally and progresses proximally to involve more muscle groups. Chorea may be hidden into or camouflaged by a voluntary movement, a phenomenon called “parakinesia”. An examination with careful observation of the patient at rest as well as during action and distraction (e.g., reading, talking, or describing a picture) is essential for identification of chorea and assessing its severity. The examination is often facilitated by seating the patient on an examination table without support for the trunk or arms, and without the legs touching the ground. Depending on the etiology, other associated features may include motor impersistence, frontal dysfunction, impaired ocular saccades, bradykinesia, rigidity and gait disturbance.

b. Classification and differential diagnosis

No specific classification system for chorea exists. It is often useful to consider the differential diagnosis and work-up of chorea in terms of age at onset – adult or pediatric.

In adults presenting with chorea:

- The most common etiology is **Huntington’s disease (HD)**, an autosomal dominant triplet-repeat genetic disorder characterized by a clinical triad of chorea, psychiatric features, and cognitive decline/dementia. The diagnosis should be suspected in any adult with chorea and a family history of similar symptoms, though the latter may not always be found. Other HD-

like neurodegenerative genetic choreas can be seen with C9orf72 repeat expansions and SCA17. HDL2 (CTG-CAG repeat expansion of junctophilin 3) is seen in individuals with black African ancestry.

- An acute onset of symptoms and unilateral distribution suggests a **vascular cause**, such as hemichorea-hemiballism associated with stroke, or non-ketotic hyperglycemia.
- **Autoimmune** forms of chorea tend to be subacute in onset, may have a fluctuating course, may be associated with other neurologic disorders, and are often not associated with eye movement abnormalities. Examples include the antiphospholipid antibody syndrome, systemic lupus erythematosus, and Sjogren's disease. Paraneoplastic chorea may be acute or subacute in presentation, may precede overt findings of cancer, and may have an associated peripheral neuropathy.
- **Chorea gravidarum** often presents during the 1st trimester of pregnancy and remits before delivery in one third of patients, or after delivery in the rest. Individuals with a past history of rheumatic fever may be more likely to experience emergence of chorea in this context.
- **Drug-induced choreas** tend to be static and non-progressive, and may occur in the context of exposure to levodopa (i.e., levodopa-induced dyskinesia), neuroleptics (i.e., tardive dyskinesia), anti-epileptics, central nervous system stimulants (e.g., chorea minima), estrogen containing oral contraceptives or lithium toxicity.
- **Other medical conditions** that can produce chorea include infectious causes such as HIV (e.g., hemichorea related to striatal toxoplasmic abscess), thyroid disorders, Wilson's disease, and polycythemia vera.
- **Paroxysmal choreas** can be seen in both kinesigenic and non-kinesigenic forms of dyskinesia and are currently classified with the dystonias, as this feature may also be present. Psychogenic causes should also be considered when paroxysmal chorea occurs.

In pediatric patients with chorea:

- **Sydenham's chorea** is the most common cause in this age group. Presence of chorea is one of the major criteria for diagnosis of acute rheumatic fever. Onset is usually 5-15 years of age after an infection such as pharyngitis or rheumatic fever, and it is more common in females. Associated features may include behavioral changes such as obsessive-compulsive behaviors and impulsivity. The course may be self-limited though severe enough to require symptomatic treatment. Prophylactic penicillin is required until age 21 to prevent recurrent rheumatic fever.
- **Autoimmune etiologies** can include the antiphospholipid antibody syndrome and systemic lupus erythematosus, similar to the adult presentation of these disorders.
- In **choreo-athetoid cerebral palsy**, a non-progressive form of chorea may result from injury to the basal ganglia and/or thalamus due to either pre- or peri-natal injuries. A static encephalopathy may exist, but intelligence is typically well preserved.
- **Inherited** causes of chorea are less common in pediatric populations. Autosomal dominant forms include the syndrome of "benign hereditary chorea" and PDE10a mutations (in which striatal lesions are seen). Autosomal recessive or X-linked genetic conditions may produce chorea as one of many neurologic features, and should be suspected when chorea occurs in combination with other abnormalities.
- **Paroxysmal choreas** may also occur, similar to the adult population.

c. Work-up

A brain MRI should be ordered in all cases, and medications and clinical history should be reviewed for any potential drug-induced or metabolic causes. Initial testing for adult-onset chorea should always include consideration of genetic testing for HD. If this initial approach is negative, but a strong clinical concern for genetic/neurodegenerative etiologies remains, then testing for other genetic causes can be considered, including C9orf72 expansions, SCA17 and HDL2. If neither of these investigations proves revealing, or if sporadic/acquired chorea is

suspected, then additional blood testing should include antiphospholipid and anticardiolipin antibodies, ANA and anti-DS DNA antibodies, and paraneoplastic antibody panel. Additional testing to consider includes a thyroid panel, ceruloplasmin, liver function tests, HIV testing, pregnancy testing, CBC/red cell mass, peripheral smear for acanthocytes, and ferritin.

In pediatric cases, testing should first be considered for streptococcal-associated symptoms, including throat culture, anti-streptolysin O titer, antiDNase B titers. An electrocardiogram and echocardiography should be performed when indicated. When negative or in cases with low suspicion for post-infectious etiologies, additional blood testing can include antiphospholipid and anticardiolipin antibodies, ANA and anti-DS DNA antibodies, thyroid function tests, blood count and ceruloplasmin.

d. Treatment

The mainstays of treatment include dopamine receptor blocking agents or dopamine depleting agents. Amantadine may have efficacy in some cases of HD. Valproic acid and carbamazepine have been described in treatment of Sydenham's chorea. Levodopa was described to improve chorea in some cases of benign hereditary chorea. Benzodiazepines such as clonazepam may have a non-specific chorea-suppressing effect, but are best not used for long-term management. Autoimmune and Sydenham's chorea may respond well to steroids or intravenous immunoglobulin (IVIg)

DYSTONIA

a. Phenomenology and Classification

The presentation and anatomic distribution of dystonia may vary by **age at onset**, and may include cranial, cervical, laryngeal, truncal, or upper/lower limb musculature. **Classification by body distribution** is particularly useful in differentiating the etiology as well as the optimal treatments strategy. In focal dystonias, only one body region or group of muscles is affected (e.g., blepharospasm or cervical dystonia). Adult onset dystonias most commonly have this phenotype. In segmental dystonias, two or more contiguous body regions are affected (e.g., craniocervical dystonias). Multifocal dystonia involves two or more non-contiguous body regions. Hemidystonia involves muscles restricted to one side of the face, arm and/or leg and often indicates a structural brain lesion in the contralateral hemisphere. Finally, in generalized forms, the trunk and at least 2 other sites are involved. Generally speaking, younger onset dystonias are more likely to be inherited in etiology and generalized in distribution. The **temporal pattern** of the disease course (i.e., static or progressive) or variability over time (i.e., persistent, action-specific, diurnal or paroxysmal) may also give clues to the etiology. For example, diurnal variation is a hallmark of dopa-responsive dystonias. Lastly the presence of other associated features such as movement disorders (i.e., isolated or combined dystonia, e.g., myoclonus-dystonia) or neurologic/systemic manifestations is also important.

b. Differential diagnosis

A few clinical syndromes should be readily recognized because they may infer specific etiologies and/or the need to pursue particular treatment strategies:

- Early-onset isolated dystonia – e.g., DYT1, DYT6, dopa-responsive dystonia
- Focal or segmental isolated dystonia with onset in adulthood – e.g., blepharospasm, oromandibular dystonia, cervical dystonia, writer's cramp, foot dystonia, dystonic camptocormia, task-specific dystonia
- Dystonia-plus syndromes
 - Dystonia-parkinsonism – dystonia in Parkinson's disease, rapid-onset dystonia-parkinsonism, X-linked dystonia-parkinsonism, neuronal degeneration with brain iron accumulation

- Myoclonus-dystonia – e.g., DYT11, DYT26
- Paroxysmal dystonias – non-kinesiogenic (DYT8), kinesiogenic (DYT18, DYT10)

In addition to these syndromes, further delineation of etiology may entail suspicion for inherited forms, acquired forms, or idiopathic forms of dystonia. In acquired dystonia, symptoms are attributed to a specific cause such as perinatal brain injury, infection, drug, toxic exposure, vascular insult, neoplastic lesion, brain injury, or psychogenic.

c. Work-up

No specific diagnostic algorithm exists for all clinical scenarios. Recognition of a dystonic syndrome rests on the presence of hallmark features, associated sensory trick(s), mirror dystonia or overflow symptoms, and possibly electromyography to differentiate other movement disorders, or distinguish dystonic tremor from other tremor types. A brain MRI should be performed in all cases to detect structural or signal abnormalities that may imply a specific diagnosis. If a dystonia clinical syndrome is identified, focused genetic or molecular investigations may be obtained.

d. Treatment

Decisions about treatment may first depend on identification of a dystonia clinical syndrome, identification of which may indicate to a specific treatment approach. Otherwise, medical treatment includes consideration of anticholinergic (e.g., trihexyphenidyl or benztropine), dopaminergic (e.g., levodopa), anti-dopaminergic (e.g., tetrabenazine), GABA-ergic (e.g., benzodiazepines), or anti-spasmodic agents. Medication management is often unsatisfactory and may lead to dose-limiting side effects that preclude an optimal response. Botulinum toxin injections are the treatment of choice for patients with focal dystonias or for relief of select postures/movements in those with more generalized forms. Intrathecal baclofen or deep brain stimulation may be efficacious for individuals with specific conditions and refractory symptoms.

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