CHOREA
VIDEODIAGNOSIS AND TREATMENT

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Chorea is derived from a Greek word, χορεία, which means "dance". It is a form of hyperkinetic movement disorder characterized by flowing quality of the movements that **randomly** flit from one body region to other. Ballism and athetosis are variations of chorea. When movements involve the proximal limb and have large amplitude, they are called "ballism". The term "Athetosis" is usually used when movements involve the distal limb and have relatively slow velocity.

Sometimes when chorea is mild, intermittent, small-amplitude and involves distal limbs, a patient may look fidgety and chorea can be missed. It is useful to examine patients when sitting and hanging their legs from the examining bed to see small movements in the feet or toes. Other phenomenological characteristics of chorea include *parakinesia* and *motor impersistence*. Parakinesia is choreic movements that patients blend into their natural movements. Motor impersistence is classically examined in the tongue or hand by asking patients to perform sustained tongue protrusion or hand grip. Patients with motor impersistence will not be able to do so for a long period of time, typically several seconds. For hand grip, patients relax after a short period of gripping, and then grip again, giving a feature of so-called "milkmaid's grip".

How to differentiate chorea from other phenomenologies?
One of the most characteristic features of chorea is *randomness*, in addition to its flowing quality. Dystonia and its motor overflow can have a flowing quality but it is generally repetitive and slower in velocity. Myoclonus is typically more sudden, jerky with high velocity, given its usual brief duration of less than 200 milliseconds. Tics are generally quick, and associated with premonitory urge and suppressibility.

How to approach chorea in the clinic?
The list of differential diagnoses of chorea is very broad. Here we offer a general practical guide to approach chorea in the clinic. The phenomenological characteristics of chorea themselves usually do not help to pinpoint the specific diagnoses except in a few circumstances (see below). Therefore, the associated clinical features, along with age group, temporal pattern (time course), family history or pattern of inheritance and prevalence play an important role in clinical approach.

A few circumstances where phenomenological characteristics of chorea will help in the diagnosis include:

Table 1. Hemichorea and oromandibular distributions as important clinical clues in chorea

Distribution of chorea as a phenomenological clue
Disorders that can present with hemichorea
Structural lesion in contralateral subthalamic nucleus, basal ganglia or corona radiata
Non-ketotic hyperglycemia
Polycythemia vera
Hyperthyroidism
Sydenham's chorea
Disorders in which chorea has predilection to oromandibular region
Tardive chorea (tardive dyskinesia)
Chorea-acanthocytosis (also typically has tongue protrusion or "feeding" dystonia)
Acquired hepatocerebral degeneration
Levodopa-induced dyskinesia in multiple system atrophy

1. Hemichorea. From the classic teaching, hemichorea points to a structural lesion in contralateral subthalamic nucleus. However, this is not always true. In fact, a lesion causing hemichorea may be in other several different areas outside the subthalamic nucleus such as contralateral basal ganglia or corona radiata. Another caveat is that hemichorea may be caused by *not only* structural lesions, but also other causes such as some cases of hyperglycemia (typically correlating with hyperintense signal at contralateral lentiform nucleus on T1-weighted MRI), polycythemia vera, hyperthyroidism and Sydenham's chorea (Table 1).

2. Chorea in lower cranial or orobuccolingual region. Some disorders have a predilection to involve orobuccolingual region and prominent distribution of chorea in this region is a helpful clue in differential diagnosis. These include tardive chorea (or so-

called “tardive dyskinesia”), chorea acanthocytosis (typically with tongue protrusion dystonia when eating or “feeding” dystonia), acquired hepatocerebral degeneration or levodopa-induced dyskinesia in multiple system atrophy (Table 1). Pantothenate kinase-associated neurodegeneration (PKAN) also tends to involve lower cranial regions but the prominent phenomenology is generally dystonia, rather than chorea.

Besides the features above, it is generally difficult to make the diagnosis based on the phenomenology of chorea alone. We suggest the following two main steps in thought process.

STEP 1. Identify sporadic (and mostly treatable) causes of chorea.

Time course is very important to differentiate sporadic from genetic causes of chorea. In general, if chorea has acute or subacute temporal profile (duration less than one year), clinicians should think about sporadic causes first, rather than genetic.

The complete list of sporadic causes of chorea is broad, and providing an exhaustive list is not our aim. Here we group them into main categories and provide some important examples as shown in Table 2.

Table 2. Examples of sporadic causes of chorea dividing grouped into 8 large categories

Category	Examples
Structural lesions	Tumors, vascular insults (e.g. ischemic, hemorrhagic stroke and vascular malformations such as Moyamoya syndrome), demyelinating lesions
Metabolic causes	Non-ketotic hyperglycemia, hypo/hypernatremia
Hematologic causes	Polycythemia vera
Infectious causes	Toxoplasmosis, HIV encephalopathy, prion diseases
Endocrine causes	Hyperthyroidism
Drug-induced chorea	Levodopa, cocaine (“crack-dancing”), anticholinergics
Autoimmune and paraneoplastic causes	Sydenham’s chorea (in children), systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), anti-CRMP5, anti-NMDA encephalitis, anti Hu
Others	Postpump chorea

Knowing **prevalence** is very helpful. For example, the most common cause of sporadic chorea in children is Sydenham’s chorea. Non-ketotic hyperglycemia is much more common in Asian population, especially in women, compared to Caucasians. Knowing **underlying disorders** such as Parkinson’s disease or HIV will help to narrow down the differential diagnosis. Generally in patients with no known underlying disorders presenting with acute/subacute chorea and no clues of focal structural lesions, the differential diagnosis on top of our list will be Sydenham’s chorea in children. In young adults, we will include anti-dsDNA, anti-phospholipid antibodies, thyroid function test and complete blood count in our investigations. For older adults, especially when presenting with subacute onset, the paraneoplastic causes and polycythemia vera should not be missed.

There are some clinical pearls that deserve special mention.

1. Sydenham’s chorea (SC) can present with hemichorea or asymmetrical chorea. This has long been known and in fact also described by Sir William Osler in his book, “Chorea and Choreiform Affections”. SC is a late complication after streptococcal pharyngitis, typically about 2 months after. Thus, patients may have elevated anti-basal ganglia antibodies or anti-DNaseB, but not anti-streptolysin-O (ASO). It is important to recognize SC to prevent cardiac complications by obtaining echocardiogram as surveillance for carditis and mitral valvulopathy, and initiate penicillin prophylaxis. Another important point is that patients with moderate-to-severe SC may benefit from immunotherapies such as intravenous steroids, intravenous immunoglobulins (IVIG) and/or plasma exchange. Although there have been no randomized controlled studies on immunotherapies in SC, we had one patient with marked improvement in chorea after 5 days of intravenous methylprednisolone and IVIG. SC can be recurrent in some cases and persistent in about 30% of cases.

2. The absence of previous diagnosis of SLE or APS should not obviate clinicians from these diagnoses, as chorea can be the first presentation of these disorders.

3. Chorea gravidarum and other hormone-induced (e.g. estrogen-induced) choreas are emergence of chorea due to change in hormonal levels such as during pregnancy or when taking oral contraceptive pills. Patients commonly have a history of Sydenham's chorea earlier in their childhood. Chorea gravidarum or hormone-induced choreas emerge in patients with underlying choreic disorders, commonly Huntington's disease or antiphospholipid syndrome. Thus, it is important to search for an underlying diagnosis in patients presenting with chorea gravidarum or hormone-induced choreas.

STEP 2. After excluding sporadic causes, identify genetic causes of chorea by taking these factors into consideration:

- **Age group**
- **Known prevalence**
- **Associated neurologic and systemic features**

Prevalence plays an important role in all areas in Medicine including chorea.

The most common cause of genetic chorea in adults is **Huntington's disease (HD)**, followed by C9orf72 disease (according to one recent European study) and SCA17. Since other causes of genetic chorea can be clinically similar to HD, they are also called "HD phenocopies". In children, the most common genetic cause is **benign hereditary chorea (BHC)**, after excluding choreo-athetoid cerebral palsy (CP). In fact, we view the diagnosis of CP with great caution, and other potential genetic/metabolic causes have to be ruled out carefully. Another caveat is not to misdiagnose children with suspected genetic chorea as HD because HD in children typically presents with parkinsonism (or so-called "Westphal variant), not chorea. For HD, clinicians should not overlook the role of genetic counseling before genetic testing, especially predictive testing, as this can pose great psychological impact and consequences to patients and other family members.

Since phenomenological characteristics of chorea may not be very useful to differentiate between these disorders, other clinical clues including ethnic background, mode of inheritance, associated movement disorders and neurologic features (e.g. parkinsonism, ataxia, seizure, neuropathy, myopathy), psychiatric abnormalities and systemic features (e.g. cardiac involvement) play an important role in diagnosis (Table 2).

Treatment of chorea

Treatment of chorea can be divided into 2 main categories: 1. Specific therapies 2. Symptomatic therapies include rehabilitation, pharmacological treatment and deep brain stimulation (DBS). It is important to identify sporadic and treatable causes of chorea, as outlined above, as specific treatment must be employed when available. For genetic causes, as we discussed in "dystonia" syllabus, one "don't miss" diagnosis is Wilson's disease. Note that even when specific treatment is available, symptomatic therapy should not be neglected. For example, in hyperglycemic chorea, the specific treatment is blood sugar control. However, choreic movements can be severe and interfere with daily activities. Thus, symptomatic treatment may be required, sometimes several months before chorea improves.

Given excess dopamine in the central nervous system as one proposed common mechanism of chorea, symptomatic pharmacological therapies have focused on reduction of dopamine in the CNS, either pre-synaptically or post-synaptically. Here we classify medications based on sites of action as follows:

1. Pre-synaptic dopamine depletors. The prototypic medication in this category is tetrabenazine (TBZ). TBZ has been approved by the FDA to treat chorea in HD in the U.S. since 2008. However, it has also been widely used off-label to treat non-HD choreas. It inhibits vesicular monoamine transporter 2 (VMAT2) enzyme, an enzyme required in transportation of dopamine into synaptic vesicles. Reserpine has the same mechanism centrally but also acts at peripheral VMAT2 enzyme, hence can cause hypotension. The main side effects of TBZ are parkinsonism and depression. This can pose therapeutic challenges in some disorders such as HD or chorea-acanthocytosis which neuropsychiatric manifestations including depression often co-exist. The dose of TBZ is usually started from 25 mg/day and increased slowly (e.g. by 12.5-25

Table 3. Genetic causes of chorea in adults and children. Huntington's disease and benign hereditary chorea are the most common causes in adults and children, respectively.

Disorder	Pattern of inheritance	Gene (protein encoded)	Clinical/neuroimaging clues (other than chorea)	Remark/Caveat
ADULTS				
Huntington's disease	AD	CAG repeat expansion in *HTT* or *IT15* gene • 36-39 repeats: reduced penetrance • ≥40: full penetrance • >60 Juvenile HD (Westphal variant with seizures)	• Adults: • **Chorea, psychiatric** (anxiety, depression, OCD) and **cognitive features** • **Forehead chorea** • **Delayed initiation of saccades (oculomotor apraxia), abnormal anti-saccade task** • Motor impersistence (tongue and milkmaid's grip) • Hung-up and pendular knee jerks • Patients can have dystonia and parkinsonism • Parkinsonism becomes more prominent upon progression (when chorea "dies out") • Gait can be complex • Children: parkinsonism (Westphal variant) and seizure.	• Founder effect in Venezuela around Lake Maracaibo, but found worldwide • Do NOT send genetic testing, especially for predictive testing, without genetic counseling!
C9orf72 disease	AD	GGGGCC repeat expansion in *C9orf72* gene	• Recently found to be the second most common cause of HD phenocopies.	• Has phenotypic variability: some patients have FTD/ALS
SCA17 (HDL-4)	AD	*TBP* (TATA-binding protein)	• **Ataxia**. Third most common cause of HD phenocopies after HD and C9orf72 disease.	
Huntington disease-like 2 (HDL-2)		CTG repeat expansion in *JPH3* (Junctophilin-3)	• **African ancestry**. Can also present with parkinsonism without chorea.	• Acanthocytes can be present in 10% of patients
Neuroacanthocytosis				• Needs special technique to detect acanthocytes in blood smear • Acanthocytes not specific to these disorders (see Table 4).
➢ **Chorea-acanthocytosis**	AR	*VPS13A* (Chorein)	• Dystonia with predilection to lower cranial region • Characteristic **"feeding" (tongue protrusion) dystonia** • Can bite lips and tongue (mimicking Lesch-Nyhan) • **Myopathy** (with elevated CK), **neuropathy**, seizure • **Psychiatric features** (depression, anxiety, OCD) • Compared to HD (anecdotally), eye movement abnormalities are not much impaired at the same stage of neuropsychiatric abnormalities • MRI: atrophy of caudate nuclei, similar to HD	
➢ **McLeod syndrome**	X-linked	*XK* (Kx antigen)	• Feeding dystonia rare. Seizure, neuropathy, myopathy, **cardiac involvement**	
Dentatorubralpallidoluysian atrophy (DRPLA)	AD	*ATN1* (Atrophin)	• Generally manifest with choreoathetosis if age at onset > 20 years • **Seizure, myoclonus, ataxia**. MRI: Pontocerebellar atrophy, white matter T2 hyperintensities	
Neurodegeneration with brain iron accumulation (NBIA)				• PKAN can also cause chorea but much less common than neuroferritinopathy and aceruloplasminemia
➢ **Neuroferritinopathy**	AD	*FTL* (Ferritin light chain)	• **Low serum ferritin** (not all cases). MRI T2*, GRE or SWI: **cystic degeneration** in caudate and putamen • "Pencil sign" (cortical lining of iron) has also been reported	
➢ **Aceruloplasminemia**	AR	*CP* (Ceruloplasmin)	• Dystonia, ataxia, **diabetes mellitus, retinal degeneration, anemia** • **ABSENT serum ceruloplasmin** (as opposed to LOW level in Wilson's disease) • Iron accumulation on T2* MRI in the striatum, thalami and dentate nuclei.	

Table 3. (continued)

Disorder	Pattern of inheritance	Gene (protein encoded)	Clinical/neuroimaging clues (other than chorea)	Remark/Caveat
CHILDREN				
Choreo-athetoid cerebral palsy	N/A	N/A	• Often co-exist with **dystonia** • Flowing component may sometimes be difficult to differentiate between dystonia and choreo-athetosis • Dystonic hand posturing which is typically not painful and is unique: difficult for normal person to mimic	• We include this into this table as it is likely a mixed bag of genetic/metabolic disorders which have to be ruled out carefully before making this diagnosis
Benign hereditary chorea (BHC)	AD	*TITF1* (or *NKX2-1* gene). Also *ADCY5* and *GNAO1*	• Also called **"brain-lung-thyroid" (or BLT) syndrome** • Hypothyroidism and pulmonary disease (e.g. respiratory distress or interstitial lung disease) can co-exist • Typically **non-progressive**, but not always "benign" (considered relatively more "benign", compared to HD) • Patients may have developmental delay or short stature.	• Some may respond to levodopa! • ADCY5, a relatively new gene, has phenotypic variability ✓ Found in previously called "familial dyskinesia with facial myokymia" (indeed NOT myokymia on EMG) ✓ Some may have dystonia or or paroxysmal nature of movements
Lesch-Nyhan syndrome	X-linked	*HPRT* (Hypoxanthine-guanine phosphoribosyltransferase)	• Often associated with **dystonia with predominant lower cranial involvement** • **Self-mutilation** • May resemble chorea-acanthocytosis but age group is typically younger • Hyperuricemia.	
Wilson's disease	AR	*ATP7B*	• Varieties of movement disorders including dystonia, parkinsonism, ataxia, tremor including classic "wing-beating" tremor (a form of cerebellar tremor; but not common) • Kayser-Fleischer rings (pay attention to upper and lower limbi); if in doubt, refer for slit-lamp exam • Low serum ceruloplasmin, low serum copper, high 24-hr urine copper	
AR ataxia				• Most of AR ataxias presenting in childhood can present with dystonia and/or chorea
Friedreich's ataxia (FA)	AR	*FXN* (Frataxin); due to GAA repeat expansion and/or mutation	• Dystonia, ataxia, pes cavus, hyporeflexia, diabetes mellitus, cardiomyopathy, scoliosis. Macrosaccadic oscillations, hypermetric saccades • Relatively preserved cerebellar size on MRI until late stage • Variants (these two overlap) ✓ FA with retained reflex (FARR) or hyperreflexia, often late onset ✓ Late-onset FA (LOFA)	
Ataxia with oculomotor apraxia type 1 (AOA1)	AR	*APTX* (Aprataxin)	• **Oculomotor apraxia** (delayed initiation of saccades) • **Neuropathy** • **Low serum albumin, high cholesterol**	• DDx of oculomotor apraxia associated with ataxia include ataxia-telangiectasia (AT), AOA1 and AOA2
Ataxia with oculomotor apraxia type 2 (AOA2)	AR	*SETX* (Senataxin)	• Age group is typically older than AOA1 • **Oculomotor apraxia** • **Neuropathy** • **High alpha-fetoprotein (AFP)** in almost all cases	• AFP can elevated in AT (almost all cases)
Metabolic disorders e.g. organic acidemia	AR	Multiple	• Can also present with **dystonia** • **Hyperintense signals at bilateral lentiform nuclei** on T2W MRI	• DDx includes methylmalonic acidemia, glutaric aciduria type I, among others • Check plasma amino acid and urine organic acid
Mitochondrial disorders e.g. Leigh syndrome or MELAS	Mitochondrial or AR (if from nuclear mutations)	Nuclear/mitochondrial gene mutations	• May also present with **dystonia** • MRI in **Leigh syndrome: hyperintense signals at bilateral lentiform nuclei** on T2W sequences • **MELAS** can have **basal ganglia calcification** (CT is useful to demonstrate)	• Start from checking high lactate level in serum and CSF

Table 4. Acanthocytes can be present in several disorders, not specific only to neuroacanthocytosis.

Disorders that acanthocytosis may be present
➢ Neuroacanthocytosis (AR form: chorea-acanthocytosis; X-linked form: McLeod syndrome)
➢ Huntington disease-like 2 (HDL2)
➢ Pantothenate kinase-associated neurodegeneration (PKAN)
➢ Abetalipoproteinemia (Bassen-Kornzweig disease)

mg/week) to the target dose of 25-150 mg/day (divided into 2-3 times a day). CYP2D6 genotyping to identify fast vs. slow metabolizers has been recommended when the dose 50 mg/day or greater is employed. Metyrosine, another dopamine depletor by inhibiting tyrosine hydroxylase, has not been widely used in current clinical practice due to its limited availability.

The new medication, deutetrabenazine (SD809), has been under clinical trials in treatment of chorea in HD. It has been claimed to have less sedation, compared to TBZ. However, it has not yet been available in clinical practice.

2. Post-synaptic dopamine receptor blocking agents. This group of medications has become less popular due to concern of the risk of tardive dyskinesia. However, they are still of clinical use, especially in countries where TBZ is not available or when TBZ is contraindicated. Two atypical neuroleptics, clozapine and quetiapine, are “cleaner” with regards to risk of tardive dyskinesia which has been reported in only few cases. Besides their paradoxical indication in treatment of tardive chorea (or tardive dyskinesia), clozapine and quetiapine have been less commonly used for symptomatic reduction of chorea. Haloperidol (a typical neuroleptic) or risperidone (another atypical neuroleptic with higher risk of tardive compared to clozapine or quetiapine) are more commonly used in chorea and possibly more effective, at least in our experience. The usual clinical doses are 0.5-2 mg/day of haloperidol, and 0.25-2 mg/day of risperidone. The side effects include parkinsonism and risk of tardive dyskinesia, due to D2 receptor blockade.

Indications of DBS in chorea are still under investigations, and not yet clearly indicated as in dystonia or Parkinson’s disease. Benefits have been reported in some patients with HD, chorea-acanthocytosis and cerebral palsy. However, it has not been performed routinely in clinical practice.

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