Acute and Chronic Chorea in Childhood

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This review discusses diagnostic evaluation and management of chorea in childhood. Chorea is an involuntary, hyperkinetic movement disorder characterized by continuous, jerky, or flowing movement fragments, with irregular timing and direction. It tends to be enhanced by voluntary actions and generally causes interference with fine motor function. The diagnostic evaluation begins with accurate classification of the movement disorder followed by consideration of the time course. Most previously healthy children presenting with acute/subacute chorea have an autoimmune etiology. Chronic chorea usually occurs as part of encephalopathies or diseases causing more global neurologic symptoms. We review the management of acute/subacute and chronic choras, with special emphasis on Sydenham chorea and benign hereditary chorea.

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Chorea is a nonpatterned, involuntary, hyperkinetic movement disorder. It is continuous, variable in speed, unpredictable in timing and direction, and flowing or jerky in appearance.1 Chorea may be accompanied by athetosis or ballism. Athetosis is also continuous but the rate is slower. Athetosis often accompanies dystonia or occurs in symptomatic chorea and may be referred to as choreoathetosis. Ballism designates larger amplitude, flinging, proximally generated movements. It rarely occurs in isolation in children but can accompany chorea.

Anatomically, chorea classically most often results from disturbances in the caudate or putamen.2 Occasionally, the source may be thalamic/subthalamic.3 A number of neurodegenerative ataxias can also present with prominent chorea.

Because of the vulnerability of the basal ganglia and its connections to a wide variety of pathologies, the differential diagnosis of acute and chronic chorea is very large. Genetic and metabolic diseases, endocrine disturbances, autoimmune disorders, infections, cerebrovascular disease, neoplasms, neurodegenerative diseases, toxins, and trauma can all result in chorea. A detailed review of the entire spectrum of these diseases would exceed space limitations for this article. This review will discuss acute and chronic chorea, emphasizing clinical diagnosis and management. Sydenham chorea, the most common acute/subacute acquired chorea in childhood, and benign hereditary chorea, a rare but primary genetic chorea, will be emphasized. Paroxysmal movement disorders involving chorea will not be discussed but are reviewed elsewhere.4 As the phenomenology of chorea overlaps in acute and chronic choreas, most features of the neurologic examination will be discussed under acute chorea.

Acute Chorea

Clinical Characteristics of Acute/Subacute Chorea

History of Present Illness

In childhood, chorea is most often acquired acutely or subacutely. It interferes with purposeful movements and often with speech. Parents can describe the hour, day, or week of onset and the way in which the child’s speech and purposeful movements have changed. In subtle cases, parents will report that coordination or speech has been affected in ways that may not be apparent to the examiner. When the observable, choreic movements are being discussed in clinic, children with mature communication and awareness should be able to describe the subjective nature of the movements, that is, the movements are involuntary, nonsuppressible, and not performed in response to an urge or sensation. They may describe that the movements make them clumsy and that their speech is slurred or slow. The movements generally cause functional interference. This can be gauged by asking about difficulties with activities of daily living.

A careful history of possible antecedents to acute chorea is critical. As the most common etiology is autoimmune and poststreptococcal, a careful history of known or possible upper respiratory infections or other illnesses should be sought. Exposures to and doses of psychiatric and other medications,
exposure to toxins, detailed medical and developmental history, recent psychological stressors, and review of systems should be routinely obtained.

**General and Neurologic Examination**

During the process of taking the history, the clinician will generally observe that the child’s trunk appears restless and is moving continuously in a random manner that is distinct from titubation seen in ataxias. The child with acute chorea may have generalized or localized dyskinetic movements. Usually, there is prominent involvement of the face and 1 or both arms and hands. Irregularly flowing or jerking, continuous movements give an appearance of restlessness. Facial and tongue chorea may slur or slow speech. Marked asymmetry of upper limb chorea may occur.

The general examination is important for other signs of illnesses, particularly those indicating autoimmune diseases and infections. Skin, heart, joints, and lymph nodes should be emphasized. Identifying an integral non-neurologic feature of a disease narrows the differential diagnosis of the movement disorder. For example, the presence of joint inflammation or a systolic cardiac murmur supports an autoimmune etiology.

The neurologic examination should be thorough, emphasizing portions of the examination related to basal ganglia and cerebellar function. The clinician should carefully observe the child’s motor system at rest as well as while performing sustained movements and common actions. Videotaping the examination is helpful to allow reviewing phenomenology and assessing severity over time. Key findings of the neurologic examination are described in Table 1.

Finally, it is important to note that fairly continuous, frequent myoclonus, particularly with dystonia, may lead to a movement disorder that appears identical to chorea.

**Diagnostic Approach**

The critical component is identifying and classifying the movement disorder. Once established that the problem is acute chorea, the history should point to a relatively limited number of categories of disease, and from there the testing can be targeted. Selected etiologies are listed in Table 2.
Differences Between Sydenham Chorea (SC) and Pediatric Autoimmune Neuropsychiatric Disorder Associated With Streptococcal Infections (PANDAS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>SC</th>
<th>PANDAS</th>
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<tbody>
<tr>
<td>Prevalence</td>
<td>Rare</td>
<td>Controversial</td>
</tr>
<tr>
<td>Cardiac involvement</td>
<td>Carditis/valvular disease occurs prior, during, or after chorea if GABHS infections recur</td>
<td>No current evidence that this occurs; published case series negative for cardiac disease</td>
</tr>
<tr>
<td>Time course and prognosis</td>
<td>Self-limited, generally resolves in &lt; 1 year</td>
<td>Explosive onset/exacerbations on 2 or more occasions, chronic symptoms may persist to a milder degree between episodes, long-term tics and/or OCD common</td>
</tr>
<tr>
<td>Effect of antibiotics on current neurologic or psychiatric symptoms</td>
<td>No suppression of symptoms reported</td>
<td>Clinicians/families often report antibiotics directly suppress the tics or OCD but no currently published clinical trials support this</td>
</tr>
<tr>
<td>Role of immune therapies</td>
<td>No accepted standard</td>
<td>Controversial</td>
</tr>
<tr>
<td>Role of antibiotics for secondary prevention</td>
<td>Standard of care, until age 21</td>
<td>Controversial</td>
</tr>
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**Diagnostic Testing**

**Laboratory Testing.** A subacute course is most common and supports an inflammatory disease, most commonly post-streptococcal. Documenting a positive culture for group A β-hemolytic streptococcal (GABHS) infection in the throat, during the previous 6 months, helps confirm a diagnosis of Sydenham chorea (SC). Otherwise, blood testing for elevations in streptococcal antibodies, anti-streptolysin O (ASO) and anti-DNase B (ADB), should be obtained, tested in an experienced laboratory, and compared against childhood normative levels for that laboratory. It should be noted that GABHS infections are highly prevalent and therefore elevated antibody titers are nonspecific. If ASO and ADB are not elevated, it is important to test for systemic lupus erythematosus and anti-phospholipid antibody syndrome. Referral to a department of rheumatology may be considered. Chorea caused by other infections, such as herpes simplex, Lyme disease, human immunodeficiency virus, mycoplasma pneumonia, or Legionnaire disease may be considered in the appropriate clinical setting, but this is extremely rare.

**Neuroimaging.** Obtaining a brain MRI scan to rule out brain structural causes should be considered as part of the evaluation of any child presenting with acute/subacute chorea. However, in most cases where the clinical diagnosis is SC, neuroimaging does not guide management. MRI findings would also point toward diagnoses of mitochondrial/metabolic diseases, degenerative, neoplastic, and other inflammatory diseases targeting the basal ganglia.

**Neurophysiology.** Electroencephalography, central motor neurophysiological assessment with transcranial magnetic stimulation, and electromyography are of interest in the field of research. These studies do not routinely guide management.

**Sydenham Chorea**

**Clinical Features**

SC is an autoimmune disease. Chorea in isolation or accompanied by other organ involvement is considered a manifestation of rheumatic disease, a group of sequelae of GABHS infections, based on Jones criteria. GABHS are Gram-positive bacteria that colonize or invade the upper respiratory tract. In selected cases, possibly due to molecular mimicry, an autoimmune response is triggered. The relationship of GABHS to SC is supported by epidemiologic observations, including the reduction in cases in the post-antibiotic era and common co-occurrence of chorea and other manifestations of rheumatic disease, particularly carditis and arthritis.

Chorea in SC develops over hours to days. Symptom severity varies widely but generally there is difficulty with fine motor tasks. Parents often report personality changes, including inattention, anxiety, obsessive compulsiveness, paranoia, and reluctance to speak. Interestingly, children with rheumatic fever not only commonly develop obsessive compulsive symptoms, they also have a higher than expected prevalence of these symptoms in first-degree relatives. Because SC is a form of rheumatic disease, it is critical to assess the child carefully for the presence of a systolic heart murmur or of arthritis or arthralgia.

The term SC should not be used interchangeably with the term pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Key distinguishing features are listed in Table 3.

Further discussion of PANDAS lies outside the scope of this review, but a number of recent studies are of interest.

**Management**

Management involves education about the diagnosis and decisions about medical treatment. There is typically no role for occupational or physical therapy.

**Secondary Prevention of Group A β-Hemolytic Streptococcal Infections.** The standard of care for all children diagnosed with SC, even in cases of isolated chorea with no carditis or arthritis, is secondary prevention with penicillin or comparable agents to reduce the risk of future GABHS infections causing permanent cardiac valvular damage.

**Chorea Symptom Suppression.** This treatment is elective. Chorea symptom suppressing medication is effective and may be used when chorea interferes with important daily activities. The use of tics or obsessive compulsive symptoms (OCD) is often considered. The use of long-term tics may persist to a milder degree between episodes, long-term tics and/or OCD common.
activities. Beneficial chorea suppression in SC has been described in small case series with benzodiazepines and several anticonvulsants, most commonly valproic acid. Some consider dopamine receptor blocking agents to be the treatment of choice, as these are usually highly effective at low doses. The expected course of treatment is brief, that is, weeks to months. Therefore, long-term tardive risks are insignificant. Anticholinergic agents should not be used.

**Immune Modulation.** This treatment is not established. On the basis of pathophysiology of SC, it is reasonable to consider immune-modulating therapies, for example, steroids or intravenous immunoglobulin (IVIG), to shorten the course of illness in severe cases. The most compelling evidence for benefit comes from steroids, and IVIG, in a recent randomized, blinded placebo-controlled study. Relative to placebo, a 2-mg/kg daily oral dose of prednisone over 4 weeks, followed by taper, reduced the duration of chorea and accelerated the reduction in symptoms. Weight gain was substantial, so a shorter treatment course may be more reasonable. Supportive evidence also comes from a clinical trial comparing prednisone to IVIG and plasmapheresis. There was no placebo group in that study. Other reports from uncontrolled, retrospectively ascertained data are difficult to interpret.

## Chronic Chorea

### Clinical Characteristics of Chronic Chorea

#### History of Present Illness

Most children with chronic chorea have a mixed movement disorder secondary to a static or progressive encephalopathy. In these cases, chorea is just 1, not necessarily predominant, symptom. Chronic chorea may emerge gradually in infancy but more commonly becomes apparent after age 1 year.

Children with chronic, early-onset choreas may have subnormal motor skills and function. In most conditions, it is more widespread central nervous system abnormalities, and not chorea per se, that are interfering with normal neurologic function. As in Sydenham chorea, children with mature communication and awareness should be able to describe the subjective nature of the movements, that is, the movements are involuntary, nonsuppressible, and not performed in response to an urge or sensation. However, awareness of the movements on an ongoing basis may be low.

A careful developmental history is critical. Progressive loss of skills requires a detailed evaluation to attempt to identify a genetic/molecular diagnosis. Although at present this will most likely not have a specific treatment, precise molecular diagnoses give families a feeling of knowledge and more control, and these may allow participation in advocacy and support groups. Problems with learning and mood should be systematically assessed as well, as these commonly co-occur. The presence of seizures with chorea generally indicates a diffuse, serious central nervous system disease.

#### General and Neurologic Examination

Many diseases cause a relatively small number of types of movement disorders. The general examination can reveal findings, for example growth parameters or dysmorphic features that narrow the differential diagnosis.

The neurologic examination should be thorough, emphasizing portions of the examination related to basal ganglia and cerebellar function. Assessment of head growth, cognitive function, speech, and cortical spinal tract function are also important, as chronic neurologic conditions with chorea often involve multiple neurologic systems.

Key findings of the neurologic examination related to chronic choreas are discussed in Table 1.

#### Diagnostic Approach

A constellation of neurologic and non-neurologic symptoms and signs can be used effectively to narrow the differential diagnosis. Selected diseases are discussed in Table 1.

#### Diagnostic Testing

Neuroimaging with brain MRI is usually a diagnostic test of choice. Decisions about genetic and metabolic testing, particularly for progressive, inherited diseases, can be informed with on-line resource, such as on-line Mendelian inheritance in Man (http://www.ncbi.nlm.nih.gov/omim) and Genetests (http://www.genetests.org).

### Benign Hereditary Chorea

#### Clinical Features

Benign hereditary chorea (BHC) is a rare, autosomal dominant, static disorder characterized by onset of chorea before age 5. “Atypical” clinical features are common and there is substantial overlap in phenomenology with myoclonus dystonia. The severity of the chorea varies substantially within and between families. Otherwise, chorea is isolated. Features supporting this diagnosis include normal general examination with no dysmorphic features, broadly normal intellectual development with no regression or loss of cognitive function.

#### Table 4: Etiology of Chronic Chorea in Childhood: Categories and Selected Examples

<table>
<thead>
<tr>
<th>Etiologic Category</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Primary</td>
<td>Benign hereditary chorea (including syndrome of choreoathetosis, hypothyroidism, neonatal respiratory distress)</td>
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<tr>
<td>Secondary</td>
<td>Stroke/third trimester or pregnancy or perinatal hypoxic ischemic injuries leading to choreoathetoid cerebral palsy</td>
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<tr>
<td>Vascular/hypoxic ischemic</td>
<td>Lesch–Nyhan syndrome, Nonketotic hyperglycinemia, Phenylketonuria</td>
</tr>
<tr>
<td>Chorea in neurodegenerative diseases and severe encephalopathies</td>
<td>Ceroid-lipofuscinosis</td>
</tr>
<tr>
<td>Diseases with chorea as a minor or late feature</td>
<td>Ataxia telangiectasia</td>
</tr>
<tr>
<td>Chorea in ataxias</td>
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</table>
skills, absence of other significant neurologic disturbances, such as epilepsy, and, with the exception of chorea, normal neurologic examination findings. As is often true in movement disorders, it is important to examine other family members in addition to taking a multigeneration history. The presence of mild symptoms in a parent would support the presence of autosomal dominant inheritance in BHC. Some symptom improvement may occur in adulthood.

In the absence of a family history, other diagnoses to consider in a child presenting under age 5 with chorea include ataxia telangiectasia (AT), which is autosomal recessive. The characteristic telangiectasias lag behind the neurologic symptoms. Initial diagnostic testing for a young child with chorea, dystonia, or ataxia emerging between 12 and 36 months of age should include serum alpha-fetoprotein, which is elevated in AT.

**Diagnosis.** MRI is usually normal. BHC is caused in some, but not all pedigrees, by mutations in the NKX2.1 gene encoding TITF1. Commercial diagnostic testing is available.

**Management.** There is no symptomatic treatment shown to be beneficial in genetically confirmed BHC. Interestingly, there is a report of improvement with levodopa treatment.

**Conclusions**

The presence of acute or chronic chorea suggests disordered neural transmission or structural pathology in the basal ganglia or occasionally in other structures. The most common causes of acute chorea in children are autoimmune, especially poststreptococcal, SC. In chronic encephalopathies, chorea usually occurs in conjunction with other neurologic symptoms.

**References**

3. Lee MS, Marsden CD: Movement disorders following lesions of the thalamus or subthalamic region. Mov Disord 9:493-507, 1994