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Topical Review

Treatment of Chorea in Childhood

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ABSTRACT

Chorea is a movement disorder characterized by ongoing random-appearing sequences of discrete involuntary movements or movement fragments. Chorea results from dysfunction of the complex neuronal networks that interconnect the basal ganglia, thalamus, and related frontal lobe cortical areas. The complexity of basal ganglia circuitry and vulnerability of those circuits to injury explains why chorea results from a wide variety of conditions. Because etiology-specific treatments or effective symptomatic treatments are available for causes of chorea, defining the underlying disease is important.

The treatment of chorea can be considered in three main categories: (1) terminating or modifying exposure to the causative agent, (2) symptomatic treatment of chorea, and (3) treatment targeting the underlying etiology. Symptomatic treatment decision of chorea should be based on the functional impact on the child caused by chorea itself. There have been no reported randomized, placebo-controlled trials of symptomatic treatment for chorea in childhood. Thus the recommendations are based on clinical experience, case reports, expert opinions, and small comparative studies. Better knowledge of mechanisms underlying childhood chorea will provide more etiology-based treatments in the future.

Definitions and phenomenology

Chorea is a movement disorder characterized by ongoing random-appearing sequences of discrete involuntary movements or movement fragments. The movements appear random because of unpredictable timing, duration, direction, or anatomic location. The duration of the individual movements is brief, typically in the range of 50 to 300 ms.[1] Although there is some overlap in duration, the movements of chorea are typically less sustained than those of dystonia and are more sustained and less "shock-like" than those of myoclonus. The presence of chorea often gives the child a "fidgety" appearance with an apparent inability to remain still.

When choreic movements are especially large in amplitude, forceful, and involve more proximal joints, resulting in flinging or flailing movements of the limbs, the term *ballism* is often used. Ballism is part of the spectrum of chorea and involves similar pathophysiologic mechanisms. When ballism effects one side of the body, it is called *hemiballism*. Hemiballism is the classical manifestation of injury affecting the subthalamic, nucleus but it can be associated with lesions in other parts of the basal ganglia.[2]

Involuntary movements that result in slow, continuous, involuntary, nonforceful, and sinuous movements of distal body parts that prevent maintenance of a stable posture are called *athetosis*. The lack of identifiable movement fragments and the involvement of same body parts repeatedly distinguish athetosis from chorea. In children, athetosis rarely occurs in isolation and often accompanies chorea or dystonia. The term *choreoathetosis* is commonly used by clinicians to describe movements that are difficult to fully classify as chorea or athetosis. Athetosis is most often observed in children with dyskinetic cerebral palsy and in many cases accompanies dystonia as a coexisting movement disorder.[2-4] Athetosis is a distinct movement disorder, but the spatiotemporal characteristics make it appear as if on a continuum between dystonia and chorea.

The term *choreiform* is often used in reference to very-low-amplitude choreic movements. We prefer the term *minimal chorea* as a more precise term that also conveys the slightness of the

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movements. Minimal chorea is often noted in children who are otherwise healthy or in those who have neurobehavioral disorders, particularly when arms are held in outstretched position.[2,3]

Pathophysiology

Chorea classically results from dysfunction of the complex neuronal networks that interconnect the basal ganglia (striatum, globus pallidus, subthalamic nucleus, substantia nigra), thalamus, and related frontal lobe cortical areas.[5] The inputs to the basal ganglia from the cerebral cortex are glutamatergic and excitatory. The majority of intrinsic basal ganglia circuitry is GABAergic and inhibitory, with modulation by peptide neurotransmitters and dopamine, and the output from the basal ganglia to the thalamus and brainstem targets is entirely GABAergic and inhibitory.[6] Structural or functional lesions that result in decreased inhibitory output from the basal ganglia can cause chorea, regardless of the specific focus of that abnormality. Lesions causing chorea are most likely to be located in the striatum or the subthalamic nucleus.[6,7] Based on the known pathophysiology and the critical roles of γ-aminobutyric acid (GABA) and dopamine, most pharmacotherapies for chorea target GABAergic or dopaminergic neurotransmission.[4] Cholinergic transmission is typically intact, so anticholinergic medications are rarely effective for chorea. In some types of chorea, dysregulated neuronal discharge in basal ganglia circuits may be present, and this may explain the efficacy of antiseizure medications in some cases.

Etiologies

The complexity of basal ganglia circuitry and vulnerability of those circuits to injury explains why chorea results from a wide variety of conditions.[4,7-11] Because of the wide diversity of etiologies for chorea, attempts have been made to develop classification systems to guide clinicians in the approach for differential diagnosis, and none of them is without shortcomings.[3,4,8-11] Traditionally, chorea has been classified as primary and secondary. The term *primary* was used interchangeably with "idiopathic" or "genetic," and *secondary* was used to mean that the chorea resulted from a known underlying disorder. This classification has diminishing utility given the rapid advances in understanding the genetic etiologies of movement disorder. Another approach classifies choreas based on the time course of symptom onset and evolution, e.g., acute, subacute, paroxysmal, chronic static, and chronic progressive. However, this is also unsatisfactory because of the phenotypic spectrum within individual disorders and lack of specificity of time course for predicting underlying cause. Similar to the etiologic classification of dystonia by Albanese et al.,[12] it may be more useful to classify chorea as acquired (known specific cause), inherited (proven genetic origin), and idiopathic (unknown cause). However, even with that scheme there is some lack of specificity because some causes of "acquired" chorea may have a genetic component.

In clinical practice, age and rapidity of onset are two important factors for prioritizing the differential diagnosis of chorea. Chorea in children most often presents with acute or subacute onset due to an acquired cause. Because etiology-specific treatments or effective symptomatic treatments are available for causes of chorea, defining the underlying disease is important. Tables 1 and 2 briefly summarize the expanding etiologic classification of childhood-onset choreas.

Treatment

The treatment of chorea can be considered in three main categories: (1) terminating or modifying exposure to the causative agent, (2) symptomatic treatment of chorea, and (3) treatment targeting the underlying etiology. Etiology-specific treatment is the ultimate goal for most conditions causing chorea in children, but at this time it is available only in a minority of conditions.

TABLE 1.
Common Acquired Causes of Childhood-Onset Chorea

Structural: Basal ganglia lesions
- Stroke
- Moyamoya disease
- Vascular malformations
- Hemorrhage
- Postpump chorea
- Mass lesions
- Choreoathetoid cerebral palsy
- Trauma

Parainfectious: Autoimmune disorders
- Sydenham chorea
- Chorea associated with antibody-mediated disorders (anti-NMDA receptor encephalitis, basal ganglia encephalitis)
- Antiphospholipid antibody syndrome
- Systemic lupus erythematosus
- Acute disseminated encephalomyelitis
- Behçet disease
- Celiac disease

Infectious disorders
- Human immunodeficiency virus encephalopathy
- Viral encephalitis (herpes simplex virus, mumps, varicella, parvovirus B19, measles)
- Legionella, mycoplasma
- Lyme disease
- Toxoplasmosis

Metabolic
- Hypo/hyperglycemia
- Hypo/hypernatremia
- Hypo/hypercalcemia
- Hyperthyroidism

Drug-induced
- Direct mechanism (dose-dependent)
  - Psychostimulants
  - Sodium channel blockers (phenytoin, carbamazepine, tiagabine)
  - Calcium channel blockers
  - Antimuscarinics
  - Others (baclofen, steroids, cyclosporine, propofol)
- Indirect mechanism (due to receptor supersensitivity)
  - Dopamine-blocking agents (withdrawal or tardive syndrome)
  - Antiparkinsonian drugs with acute/chronic treatment (L-dopa-induced dyskinesia)
- Others
  - Oral contraceptives
  - Polypharmacy for psychiatric conditions or epilepsy
  - Selective serotonin reuptake inhibitors
  - Valproate

Toxin-induced
- Carbon monoxide
- Carbon disulfide
- Methanol
- Manganese
- Toluene

Psychogenic

Terminating or modifying exposure to the causative agent

Several drugs have been reported to cause chorea in childhood. Some of these cause chorea as a dose-dependent side effect, whereas the others interact with pre-existing basal ganglia network dysfunction. Examples of the latter include dopamine receptor supersensitivity or presynaptic dysfunction of dopamine neurons. A classic example is levodopa-induced dyskinesia (LID) in Parkinson disease (PD). LID may also occur in patients with tyrosine hydroxylase (TH) deficiency and other inherited disorders of dopamine synthesis despite the lack of nigrostriatal degeneration.[13]

TABLE 2.
Common Inherited Causes of Childhood-Onset Chorea

Disease	Inheritance	Associated Gene
Chorea as the core or initial feature		
Benign hereditary chorea	AD/*de novo*	*NKX2-1*
ADCY5-related dyskinesia	AD/*de novo*	*ADCY5*
PDE10A-related hyperkinetic disorder	*De novo*/AR	*PDE10A*
Adolescent-onset Huntington disease	AD	CAGn in *HTT*
Huntington disease-like 3	AR	Linked to 4p15.3
Huntington disease-like 4 (spinocerebellar ataxia 17)	AD	CAGn or CAAn in *TBP*
Ataxia telangiectasia	AR	*ATM*
Ataxia telangiectasia-like disorder	AR	*MRE11A*
Ataxia with oculomotor apraxia 1 and 2	AR	*APTX*
Friedreich ataxia	AR	GAAn in *FRDA*
Idiopathic basal ganglia calcification, childhood onset	AR and AD	*SLC20A2-PDGFRB*
Choreoacanthocytosis	AR	*VPS13A*
Paroxysmal nonkinesigenic dyskinesia	AD	*MR1*
Chorea as a common additional feature		
GLUT1 deficiency syndrome	AD	*SLC2A1*
Cerebral creatine deficiency syndrome 2	AR	*GAMT*
Pyruvate dehydrogenase E1-alpha deficiency	X-linked	*PDHA1*
Dopamine transporter deficiency syndrome	AR	*SLC6A3*
Infantile bilateral striatal necrosis	AR	*NUP62*
Congenital Rett syndrome	AD	*FOXG1*
Chorea associated with epilepsy or developmental delay	AD	*GNAO1, SCN8A, SYT1*
	AD or AR	*GRIN1*
	AR	*FRRS1L, GPR88*
Chorea sometimes present		
Dentatorubropallidoluysian atrophy	AD	CAGn in *atrophin-1*
Alternating hemiplegia of childhood	AR	*ATP1A-3*
Pantothenate kinase-associated neurodegeneration	AR	*PANK2*
Wilson disease	AR	*ATP7B*
Lesch-Nyhan disease	X-linked	*HPRT*
Phenylketonuria	AR	*PAH*
Biopterin-deficient hyperphenylalaninemia	Usually AR	*Multiple genes*
Nonketotic hyperglycinemia	AR	*GLDC, GCST or GCSH*
Glutaric aciduria type 1	AR	*GCDH*
3-Methylglutaconic aciduria type III (Costeff syndrome)	AR	*OPA3*
Succinate semialdehyde dehydrogenase deficiency	AR	*ALDH5A*
GM1-GM2 gangliosidosis	AR	*GLB1-HEXA*
Paroxysmal kinesigenic dyskinesia	AD	*PRRT2*
Paroxysmal exercise-induced dyskinesia	AD	*SLC2A1*

Abbreviations:
AD = Autosomal dominant
AR = Autosomal recessive

Unlike LID in PD, LID in TH deficiency occurs within a few days or months of treatment onset.

Another disorder that is thought to be related to dopamine D2 receptor supersensitivity is tardive dyskinesia (TD), which occurs in some patients after chronic treatment with dopamine receptor antagonists. TD is rare in children but a related disorder; withdrawal-emergent dyskinesia is more common. In that condition, rapid discontinuation of dopamine receptor antagonists is thought to result in transient overstimulation of dopamine D2 receptors.[4,7]

Estrogen-containing oral contraceptives may also induce chorea in patients with previous Sydenham chorea (SC), chorea gravidarum, antiphospholipid antibody syndrome (APS), and systemic lupus erythematosus (SLE).[4]

When chorea is caused by an exogenous toxin that is not used for therapeutic purposes, eliminating exposure is the logical course of action. When drug-or toxin-induced chorea occurs, withdrawal or dose modification of the offending agent may not always result in resolution of the symptoms. Specific pharmacologic treatments for persistent drug-induced chorea are discussed below.

Symptomatic treatment of chorea in children

Symptomatic treatment decision of chorea should be based on the functional impact on the child caused by chorea itself. If chorea is impairing, then the next step is to decide which treatment would fit the patient best. There are limited studies of symptomatic treatment for chorea in adults, and even fewer studies of childhood chorea treatment. To date, there have been no reported randomized, placebo-controlled trials of symptomatic treatment for chorea in childhood. Thus, our recommendations are based on clinical experience, case reports, expert opinions, and small comparative studies. Most of these published reports concern SC. The medications described below may be effective in multiple forms of chorea, but individual patient factors should be considered in prioritizing the choices. Tables 3 and 4 summarize the drugs used for the symptomatic treatment of chorea in children.

Dopamine-depleting agents

These agents act by reversibly and selectively inhibiting presynaptic vesicular monoamine transporter type 2 (VMAT2), which results in degradation of dopamine by monoamine oxidases before uptake into synaptic vesicles, causing dopamine depletion.[81] Although the use of dopamine-depleting agents in choreas other than Huntington disease (HD) and TD is still off-label in the United States, the advantage of dopamine depletors not causing TD with fewer side effects has led them to be preferred to antidopaminergic drugs by many clinicians.

Tetrabenazine

Tetrabenazine (TBZ) was the first dopamine-depleting agent approved by the US Food and Drug Administration (FDA) for the treatment of chorea related to HD. TBZ has a five to seven hour half-life that requires three times daily dosing in most patients, and has potential side effects including depression, parkinsonism, and akathisia.[11] Deutetrabenazine and valbenazine are other currently available dopamine depletors with longer half-lives of nine to 10 hours and 15 to 22 hours, respectively.[82,83] These drugs may cause fewer side effects due to lower peak-dose concentrations with comparable “area under the curve.” Deutetrabenazine has been approved by the FDA both for HD and TD; valbenazine is FDA-approved for TD only. Neither of these longer-acting forms has been studied in childhood chorea.

TBZ can suppress chorea even when dopamine receptor antagonists are ineffective. In a study evaluating the effect of TBZ therapy in pediatric hyperkinetic movement disorders resistant to other medications, 18 of 31 children with hyperkinetic movement disorders had chorea, nine of whom had isolated chorea.[14] Fourteen of 18 (78%) showed an improvement with TBZ. Sedation was the most common side effect, occurring in 50% of those treated, followed by behavioral changes (21%), depression (7%), oculogyria (7%), drooling (7%), nausea, and vomiting (7%). In that study, no TD occurred and parkinsonism occurred in one patient (3%) in a dose-dependent manner. The most significant finding in this study was that they used TBZ at higher doses (average 107 mg/day) than used in most adult studies (75 mg/day or less) with better apparent tolerability. In another study,[15] five children with severe chorea responded to TBZ with complete resolution in three. In that report, as much as

TABLE 3.
Drugs Used in the Medical Treatment of Childhood Chorea Due to a Variety of Conditions (see Text for Specific Comments)

Drug	Dose	Side Effects	Contraindications	Special Points	Evidence
Dopamine-depleting agents					
Tetrabenazine	Initial dose: 6.5-12.5 mg daily, increase by 12.5 mg/day every 3-5 days Usual effective dose: 50-150 mg/day, divided into three doses Maximum recommended dose: 200 mg/day	Parkinsonism, drowsiness, fatigue, sedation, anxiety, depression, akathisia, tremor, nausea, vomiting, insomnia, orthostatic hypotension, suicidality, neuroleptic malignant syndrome	History of depression, suicidality, parkinsonism, hepatic impairment Should be discontinued promptly at the first signs of depression	Children may require higher doses than adults Do not initiate therapy within 14 days of MAO inhibitor use	Retrospective studies, case series, case reports[14-23]
Reserpine	Initial dose: 0.25 mg/day Increase by 0.25 mg/day every few days Can be given in dosages of 1-9 mg/day, three times daily	Sedation, orthostatic hypotension, depression, drug-induced parkinsonism, insomnia, anxiety, akathisia, cardiac arrhythmia	Depression, Parkinson disease, orthostatic hypotension, and pregnancy	Usually reserved for patients with severe tardive dyskinesia and hemiballismus Should not be used concurrently with MAO inhibitors	Case reports for Sydenham chorea[24,25]
Potent D2 receptor blockers (typical antipsychotics)					
Haloperidol	Initial dose: 0.25-0.5 mg/day (evening) Increase 0.25-0.5 mg weekly, one or two times daily Total daily dose ranges: 0.75-5 mg	Extrapyramidal reactions, neuroleptic malignant syndrome, parkinsonism, tardive dyskinesia, drowsiness, agitation, insomnia, confusion, headache, seizures	Prolonged QT syndrome, narrow-ankle glaucoma, parkinsonism, severe cardiac or liver disease, severe CNS depression, history of extrapyramidal symptoms or neuroleptic malignant syndrome	Possible increased sensitivity in SC and NMDAR-encephalitis Should be reserved for severe cases and used with caution	Retrospective comparison studies, retrospective case series, case reports[26-33]
Pimozide	Initial dose: 0.5-1 mg/day (evening), may be increased every 5-7 days Usual range: 2-4 mg/day, two times daily Do not exceed 10 mg/day	Sedation, dysphoria, constipation, dry mouth, cognitive blunting, school refusal, acute anxiety with somatizations, personality change, weight gain, orthostatic hypotension, blurred vision	History of cardiac arrhythmias, prolonged QT syndrome, neuroleptic malignant syndrome, tardive dyskinesia, CNS depression or Parkinson disease	An ECG should be done at baseline and periodically during the dose adjustment Avoid consumption of grapefruit juice Use smallest dose with shortest duration	Retrospective comparison study Case reports[28,34-38]
Chlorpromazine	Initial: 0.5 mg/kg/dose every 4-6 hours as needed Maximum recommended daily doses: Children <5 years: 40 mg/day, IM or 50 mg/day orally Children ≥5 years: 75 mg/day IM or 200 mg/day orally	Anticholinergic effects, sedation, somnolence, CNS depression, extrapyramidal side effects, hypotension, QT prolongation, blood dyscrasias	Hypersensitivity to phenothiazines, concomitant use with large amounts of CNS depressants, comatose states	Use with caution in patients with cardiovascular disease, avoid use in patients suspected to have Reye syndrome	Retrospective comparison, case reports[30,39-43]
Atypical antipsychotics					
Risperidone	Initial dose: 0.25 or 0.5 mg/day (evening) and titrate up to 2-4 mg/day gradually, two times daily	Hypotension, somnolence, weight gain, hyperglycemia, akathisia, parkinsonism, tremor, neuroleptic malignant syndrome, headache, seizures	History of QT prolongation, use of other drugs known to prolong QT interval, caution is recommended when there is concern for hyperglycemia and diabetes	Use smallest dose with shortest duration	Prospective open-label study, expert opinion[44,45]
Antiepileptic drugs					
Valproic acid	Initial dose: 10-15 mg/kg/day or 125 mg, two times daily Increase by 5 to 10 mg/kg weekly up to 25-30 mg/kg/day or 1000 mg/day	Nausea, vomiting, weight gain, drowsiness, tremor, ataxia, hyperammonemia, nystagmus, alopecia hepatic injury, pancreatitis, Stevens–Johnson syndrome, bone marrow suppression, polycystic ovary disease	Hepatic dysfunction, urea cycle disorders, children younger than 2 years	Liver function tests should be monitored Avoid use of sodium valproate in women of childbearing age	Prospective and retrospective comparison studies, case series, case reports[29,46-56]
Carbamazepine	Initial dose: 7-10 mg/kg/day, two times daily Usual dose range: 10-30 mg/kg/day, three times daily	Dizziness, nausea, drowsiness, fatigue, unsteadiness, blurred vision, weight gain, rash, hepatotoxicity, pancreatitis, and hyponatremia Serious side effects: bone marrow suppression and skin reactions	History of bone marrow suppression or known hypersensitivity to tricyclic antidepressants	Paroxysmal dyskinesias typically respond to doses less than necessary for seizure control Need to monitor liver function tests, complete blood count, sodium levels	Prospective and retrospective comparison studies, case series, case reports[29,57-61]

Abbreviations:
CNS = Central nervous system
ECG = Electroencephalography
IM = Intramuscular
MAO = Monoamine oxidase
NMDAR = *N*-methyl-D-aspartate receptor
SC = Sydenham chorea

TABLE 4.
Drugs Reported to be Effective in the Medical Treatment of Childhood Chorea Due to Specific Conditions

Drug	Dose	Side Effects	Contraindications	Specific Etiology	Evidence
Olanzapine	Initial dose: 2.5 mg/day (evening), escalate gradually as necessary up to 5-10 mg/day, two times daily	Hypotension, somnolence, weight gain, dizziness, hyperglycemia, akathisia, parkinsonism, neuroleptic malignant syndrome, seizures	Caution is recommended when there is concern for hyperglycemia and diabetes	Sydenham chorea	Case series[62]
Levetiracetam	Initial dose: 15-20 mg/kg/day or 250-500 mg/day, two times daily Anticonvulsant dose range: 20-60 mg/kg/day	Somnolence, dizziness, headache, emotional irritability, depression/suicidality, psychosis, pancreatitis, pancytopenia	Hypersensitivity, lower doses should be used in patients with impaired renal function	Dyskinetic cerebral palsy, Sydenham chorea, paroxysmal nonkinesigenic dyskinesia	Case reports[63,64]
Topiramate	Initial dose: 25 mg/day, titrate slowly Usual effective dose range: 5-9 mg/kg/day or 50-300 mg/day, two times daily	Confusion, cognitive impairment, paresthesias, ataxia, diplopia, somnolence, weight loss, nephrolithiasis, oligohidrosis, hyperthermia	Use lower doses in renal impairment	Paroxysmal kinesigenic choreoathetosis and *GNAO1*-related chorea	Open-label prospective study, case report[65,66]
Clonazepam	Initial dose: 0.25-0.5 mg at bedtime Usual dose: 1-4 mg/day, three times daily	Sedation, somnolence, fatigue, confusion, cognitive impairment, hyperactivity, ataxia	Significant liver dysfunction, respiratory depression, acute narrow-angle glaucoma	Paroxysmal nonkinesigenic dyskinesias, SLC6A3-related chorea	Case reports[67-69]
Gabapentin	Initial dose: 10-15 mg/kg/day, three times daily Usual dose: 50-300 mg/day	Sedation, dizziness, weight gain, vision changes, depression, suicidal behavior, ideation	Hypersensitivity	Hemichorea/hemiballismus	Case report[70]
Acetazolamide	Initial dose: 125-250 mg/day divided into two to four daily doses Daily dose may range 1000-2000 mg	Drowsiness, dizziness, fatigue, paresthesias, tinnitus, electrolyte imbalance, Stevens–Johnson syndrome	Hyponatremia, hypokalemia, hyperchloremic acidosis, adrenocortical insufficiency	Paroxysmal kinesigenic dyskinesia and ADCY-5-related dyskinesia	Case reports[71-73]
Methylphenidate	Initial dose: 10 mg/day, two or three times daily (30 minutes before meals) Usual dose: 10-60 mg/day	Tachycardia, hypertension, palpitations, sweating, irritability, anorexia, tremors, seizures	MAO inhibitor use, structural heart defects, hyperthyroidism, history of drug abuse	Benign hereditary chorea and ADCY5-related chorea	Case reports[66,74-76]
Levodopa	Initial dose: 1 mg/kg/day, three times daily Usual dose: 4-5 mg/kg/day (30 minutes before meals)	Nausea, vomiting, confusion, dizziness, somnolence, orthostatic hypotension, dry mouth, constipation, depression, insomnia	MAO inhibitor use, narrow-ankle glaucoma, melanoma	Benign hereditary chorea	Case reports[22,77,78]
Amantadine	Initial dose: 50 mg/day Increase 50 mg twice a day after 1-2 weeks Usual dose: 50 mg 2-3 times/day Alternative dose: 5-7 mg/kg/day	Anticholinergic-type side effects including dry mouth, nose, and throat; blurred vision; nausea; constipation; confusion; sedation	Hypersensitivity, use with caution in patients with congestive heart failure and renal insufficiency, dementia, psychosis	Ataxia telangiectasia	Open-label prospective study[79]
L-Thyroxine	Depends on age, usual dose for adolescents: 1-3 μg/kg/day (once before breakfast)	Fatigue, weight loss, headache, hyperactivity, tremor, muscle weakness, palpitations, tachycardia	Overactive thyroid gland	Benign hereditary chorea	Case report[80]

250 mg total daily dose of TBZ was administered (17 mg/kg/day) with a mean dose of 190 mg/d (14 mg/kg/day). Thus, TBZ may be tolerated by children in doses higher than those used in adults.

TBZ has been reported to be effective in specific etiologic subgroups of childhood-onset chorea including various genetic, metabolic, and immune etiologies.[16-21] TBZ has also been suggested as a first-line drug for benign hereditary chorea (BHC), the most common cause of childhood-onset genetic chorea, due to *TITF1*/*NKX2-1* gene mutations.[22,23]

- To achieve effective treatment with TBZ while minimizing side effects in childhood chorea, start at a low dose (6.25 mg to 12.5 mg per day), increase gradually in a three times per day dosing schedule, and base maximum daily dosing on magnitude of benefit and side effects.

Reserpine

Reserpine inhibits VMAT1 (peripheral) and VMAT2 (central) at the presynaptic membrane, resulting in the depletion of the synaptic pool of monoamines. This drug was used before 1990s for the treatment of SC in children.[24,25] However, the higher incidence of peripheral side effects including orthostatic hypotension, cardiac arrhythmia, and gastric intolerance due to its nonspecificity regarding central and peripheral VMAT receptors and the introduction of new drugs with safer profiles has limited its use in children more recently. Reserpine should be reserved for patients with severe TD or dystonia that is unresponsive to other treatments.

Dopamine D2 receptor-blocking agents

These agents have been known to be effective in pediatric chorea since the 1950s.[39,40,84] However, there have been no placebo-controlled trials of either typical or atypical antipsychotic agents in childhood chorea; their use is still based on retrospective studies and case series.

There are two major groups of D2 receptor-blocking agents: (1) typical or first-generation antipsychotics that are potent D2 receptor blockers (neuroleptics) and (2) atypical or second-generation antipsychotics that are dopamine-serotonin antagonists, with high affinity for 5-hydroxytryptamine 2A receptors.

General principles for D2 receptor-blocking agents can be summarized as follows:

- More potent D2 receptor-blocking action is associated with greater antichoreic efficacy
- More potent D2 receptor-blocking action is associated with a higher risk of developing TD.

Contrary to the historical thought that the percentage of D2 receptor occupation is related to the risk of TD, it appears that strength of binding to the D2 receptor better explains why atypical neuroleptics have fewer side effects despite their high D2 occupancy.[85,86]

Potent D2 receptor-blocking agents (typical antipsychotics)

Agents such as haloperidol, pimozide, and chlorpromazine were the most common therapeutic agents used to treat SC before the 1980s.[26,27,39,40,84] However, their unacceptable side effects such as acute dystonic reactions, akathisia, TD, parkinsonism, prolonged QT, sedation, and cognitive impairment limited their use in children.[41,87] After the 1980s, they became less preferred with the rapid discovery of effective and more reliable drugs.

Haloperidol. Haloperidol is a butyrophenone first-generation antipsychotic agent. The clinical experience of its use in children is mostly based on patients with SC with one prospective comparison study, one retrospective comparison study, several case series, and case reports.[26-30] In 2007, Tumas et al.[30] retrospectively analyzed the medical charts of 100 patients with SC. Of the 100 patients 82 received haloperidol with benefit and no reported significant side effects. However, Pena et al.[29] compared haloperidol, valproic acid, and carbamazepine in 18 individuals with SC prospectively and reported that two of six patients who received haloperidol developed serious side effects such as excessive somnolence and dystonic reaction, whereas no side effects were recorded with the other drugs. In a retrospective study by Demiroren et al.,[28] it was concluded that haloperidol not only seemed to be more effective than pimozide but also caused more frequent and serious adverse effects like dystonia, parkinsonism, sleepiness, and forgetfulness. Haloperidol has been reported to be effective in various other types of chorea including APS, SLE, and postpump chorea.[31-33] Potential extrapyramidal side effects of haloperidol explain why reports of haloperidol use in childhood chorea were mainly published before 2000. Despite the disadvantages, given its efficacy for chorea, haloperidol should still be considered an option for treating childhood chorea particularly in resistant cases. Careful monitoring for potential side effects is essential.

Pimozide. Pimozide is a diphenylbutylpiperidine first-generation antipsychotic drug. There is one retrospective comparison study and a few case reports for the use of pimozide in children with SC.[28,34,35] The retrospective study compared haloperidol and pimozide with respect to their efficacy and side effects.[28] Haloperidol provided a significantly faster improvement in chorea but was associated with more withdrawals due to side effects, compared with pimozide. Pimozide was also reported to be effective in moyamoya disease, cavernous hemangioma, and postpump-related chorea.[36-38] The extrapyramidal side effects of pimozide are fewer than those of haloperidol, but potential cardiac side effects of prolonged QT and arrhythmia limit its use in children.

Chlorpromazine. Chlorpromazine was the first antipsychotic drug discovered in 1950 and is considered as one of the greatest advances of the twentieth century medicine. The use of this drug in children with SC was first published in 1956.[42] Following this report, chlorpromazine was used in a few studies with inadequate information on dosing and efficacy.[39,40,88] In the study by Tumas et al.,[30] among 100 cases with SC, only one received chlorpromazine and responded well. Teixiera et al.[41] compared the side effect profile of chlorpromazine between patients with SC and those with Tourette syndrome with the hypothesis of increased susceptibility of patients with SC for extrapyramidal side effects. The investigators concluded that individuals with SC were more prone to develop extrapyramidal side effects, but the limited demographic data of the groups made it difficult to comment on this result. In 2007, Weiner and Normandin[43] reported a nine-year-old girl with SC who improved with 50 mg three times daily dosing of chlorpromazine. Chlorpromazine may be effective in childhood chorea, but it has no obvious superiority over other potential treatments.

Atypical (second-generation) antipsychotics

These drugs were first introduced with clozapine in 1990[89]; they are often preferred due to their lower risk of TD. However, the lower risk of TD may correspond to lower efficacy for chorea. Agents with higher potency at D2 receptors are more likely to be effective. Olanzapine and risperidone have been recommended for the treatment of SC.[44,62] Recently, Kamate et al.[45] studied the effect of risperidone on 30 children with choreoathetoid cerebral palsy. The investigators reported a statistically significant decline in abnormal movements, improvement in quality of life and positive change in behavior without significant side effects. Although the limited number of reports makes it difficult to comment on their use in childhood chorea, atypical antipsychotics may be considered as a treatment option and prioritized in children with behavioral comorbidities. We recommend the following considerations:

- Haloperidol is an effective antichoreic agent with high potential for side effects; therefore it should be reserved for severe cases and used with caution.
- Pimozide has fewer neuropsychiatric side effects but has a higher risk for cardiac side effects of arrhythmia and prolongation of the QTc interval.
- Atypical antipsychotic agents may also be effective and may be preferred in children with psychiatric comorbidities including FDA-approved indications.

Levodopa (L-dopa)

L-Dopa is the immediate precursor to dopamine in the synthetic pathway. Despite the fact that treatment with L-dopa worsens chorea in most conditions and may cause LID, treatment with L-dopa, may be effective in BHC due to *TITF1/NKX2-1* gene mutations.[22,77,78] BHC is possibly the only form of chorea that is likely to respond to L-dopa. Although the mechanism is unclear, a lack of functional TITF-1 protein might impair developmental maturation of the dopamine pathways in the basal ganglia.[90]

Antiepileptic drugs

These drugs are commonly used for the treatment of hyperkinetic movement disorders in children[91]; their primary mechanism of action is thought to be increasing brain GABA levels either with sodium channel blockage or with a GABA agonist effect.[86] Valproic acid and carbamazepine are the two most common antiepileptic drugs used to treat childhood chorea associated with various diseases such as SC, kernicterus, vascular, hypoxic, and traumatic chorea.[26,27,35-38,41]

Valproic acid

Valproic acid was first used for the treatment of chorea in a 19-year-old-patient with SC in 1981.[46] In the following years, several cases and case series reporting efficacy of valproate for chorea

related to various etiologies were published.[47-55] In a retrospective comparison study by Pena et al.,[29] valproic acid was found to be more effective than carbamazepine and haloperidol. Genel et al.[56] prospectively compared valproic acid and carbamazepine and reported that they are equally effective and safe. As a result, valproic acid is one of the first-line therapeutic options for the treatment of chorea in childhood. However, its long-term side effects on bone metabolism, increased risk of polycystic ovary syndrome, and teratogenic effects should be kept in mind in children and adolescents, particularly the ones who may require longer treatment duration.

Carbamazepine

Carbamazepine is the treatment of choice in chorea associated with paroxysmal kinesigenic dyskinesia (PKD).[57-59] In addition to the comparison studies of carbamazepine use in SC described above, the efficacy and safety of carbamazepine in SC is supported by other case reports and case series.[60,61] These findings make carbamazepine one of the more preferred antichoreic agents in childhood chorea along with TBZ and valproate.

Other antiepileptic drugs

Other antiepileptic drugs are known to be effective in different etiologic subgroups of chorea. Other than carbamazepine, phenytoin, phenobarbital, gabapentin, topiramate, oxcarbazepine, valproic acid, and lamotrigine have also been used in PKD.[57-59,92-94] Levetiracetam has been reported to be effective in one individual with SC and two patients with choreoathetoid cerebral palsy[63,64]; it has also been reported effective in two children with genetically confirmed paroxysmal nonkinesigenic dyskinesia (PNKD).[95] Gabapentin has been reported to be effective for hemichorea/hemiballismus.[70] In one individual with *GNAO1*-related resistant chorea, topiramate significantly reduced the frequency of chorea episodes.[96]

Mutations in several genes (e.g., *PRRT2*, *GNAO1, FOXG1, SCN8A, GRIN1*) have been associated with both chorea and epilepsy.[97-100] The increasing awareness of this association may favor the use of antiepileptic drugs in childhood chorea to treat two different conditions with a single drug to prevent multidrug use and related side effects. However, evidence is still lacking to determine whether this is the best approach.

Although antiepileptic drugs may be effective for treating chorea, these drugs, especially at high doses or in combination, may also cause chorea. A significant increased risk is described with the combined use of phenytoin and lamotrigine.[101,102] This possibility should be kept in mind in the setting of acute-onset chorea in individuals with newly initiated antiepileptic medication either alone or combination.

Although there is no consensus for the use of antiepileptic medications in childhood chorea, we provide the following recommendations:

- Valproic acid and carbamazepine may be preferred first-line agents for treating chorea, especially SC.
- Carbamazepine is the treatment of choice in PKD.
- The coexistence of epilepsy and chorea in an individual patient may be a reason to consider antiepileptic drugs as first-line agents for treating the chorea.

Benzodiazepines

Benzodiazepines, especially clonazepam, may be beneficial for treating chorea due to a variety of causes. Most of the published reports of clonazepam for treating chorea are in patients with PNKDs.[57-59,103,104] SLC6A3-related dopamine transporter deficiency syndrome is another disorder for which benzodiazepines may be beneficial to reduce chorea and other dyskinesias.[65]

Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor that has been reported to be effective for reducing symptoms in paroxysmal disorders such as episodic ataxia, periodic paralysis, and spinocerebellar ataxia type 6. Although treatment of paroxysmal dyskinesias has been less beneficial, acetazolamide has been reported to be effective to some extent in patients with chorea secondary to PKD, paroxysmal exertional dyskinesia (PED), and *ADCY-5* related dyskinesia.[67-69,105,106]

Methylphenidate

Methylphenidate is a dopamine reuptake blocker that increases synaptic concentrations of dopamine. It may seem illogical that methylphenidate might reduce choreas, but it has been reported to be effective in BHC.[74] Similar to the effect of L-dopa on *NKX2-1/TITF1* gene disorders, the exact mechanism of its benefit remains unknown.[66,75] In a recent study by Tubing et al.,[76] methylphenidate was found effective in two patients with *NKX2-1* and *ADCY-5* gene-related chorea with additional attention-deficit/hyperactivity disorder. These findings raise the possibility that methylphenidate may be a treatment option in patients with chorea and concomitant attention-deficit/hyperactivity disorder.

Amantadine

Amantadine is a noncompetitive *N*-methyl-D-aspartic acid (NMDA) receptor antagonist acting as an antiglutamatergic agent. The mechanism of action of this drug on dopaminergic system is not well understood. In adults, amantadine is the treatment of choice for LID in PD. In childhood, it was used with some benefit in a single study of ataxia telangiectasia with motor impairment including chorea.[79]

L-Thyroxine

This drug was recently reported in a single individual with BHC, asymptomatic hypothyroidism, and arm chorea. Discontinuation of L-thyroxine after a long period of euthyroid status resulted in drop attacks and reemergence of upper limb chorea. These symptoms resolved after reinitiation of L-thyroxine replacement therapy.[80]

Deep brain stimulation

Deep brain stimulation (DBS) has been used to treat a variety of movement disorders for the past two decades. Although DBS is more commonly and effectively used in childhood for primary dystonia, it may be an effective alternative treatment for medically intractable chorea. DBS treatment has been reported in dyskinetic cerebral palsy, *ADCY-5*-related dyskinesia, and *GNAO1*-related severe choreoathetosis, with variable outcomes.[71,72,107-109] Uncertainty of case selection criteria, optimal age at procedure for the best benefit, and outcome-predicting factors require additional research.[73,110]

Specific paroxysmal dyskinesias

Some of the paroxysmal dyskinesias have been shown to respond to specific medications; this is true for the most common forms of PKD, PNKD, and PED. As described above, carbamazepine is the treatment of choice in PKDs.[57-59] Proline-rich

transmembrane protein-2 (*PRRT2*) gene mutations may present with a wide range of neurological conditions including benign familial infantile epilepsy, infantile convulsions and choreoathetosis, PKD, episodic ataxia, and familial hemiplegic migraine.[111-114] Huang et al.[115] reported that 98.4% of patients with PRRT2 mutations who received carbamazepine displayed a good response. Carbamazepine may also be effective in PKD due to other causes (secondary PKD).[58,60] PNKD typically does not respond to carbamazepine, but it has been shown to respond to benzodiazepines, with most reports specifying clonazepam.[103,104] PED due to *SLC2A1* mutations (GLUT1 deficiency) does not consistently respond to either carbamazepine or clonazepam, but it may respond in some patients to acetazolamide or the ketogenic diet.[105,106] The response of paroxysmal dyskinesias due to other causes may be more variable.

Other agents

Recently, there has been growing interest in the potential for *cannabinoids* to treat a variety of movement disorders. Cannabinoids modulate the dopaminergic system through cannabinoid receptors (CB1), and the endocannabinoid system is involved in the basal ganglia pathways that are responsible for the generation of chorea.[86,116,117] However, in a systematic review published in 2017, the evidence to support the use of cannabinoids in childhood was found insufficient in conditions other than chemotherapy-related nausea, vomiting, and epilepsy.[118] Thus, there is currently no evidence to support the use of cannabinoids in any movement disorders in childhood.

Treatment targeting the underlying etiology

Etiology-based treatment of chorea may include pharmacologic, surgical, and dietary interventions. Some specific conditions in which chorea is a prominent feature and treating the underlying disease results in resolution or improvement of chorea are discussed below. The specific treatment of inborn errors of metabolism resulting in chorea is beyond the scope of this review.

Sydenham chorea

The pathophysiology of SC raises the possibility of immune-modulating therapies such as corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis, and rituximab being effective. The overall clinical experience to support the use of immunomodulatory therapies in SC is limited. Steroids have the strongest data with a prospective, double-blind randomized controlled trial and prospective or retrospective case series having been reported.[119-121] In an open-label randomized study by Garvey et al.,[122] IVIG, plasma exchange (PLEX), and oral prednisone were compared. Although clinical improvements appeared to be more rapid and robust in the IVIG and PLEX groups than in the prednisone group, the between-group differences were not statistically significant. The potential side effects, the limited scientific evidence, and the fact that SC usually improves with symptomatic therapy and resolves spontaneously have led to a tendency to reserve these alternatives for difficult to manage patients such as those with chorea paralytica.[87,119-122] However, the underlying autoimmune basis for SC provides rationale for these treatments. It should be noted that although the primary aim is to protect the heart and its effect on chorea relapses is still not clear, secondary prophylaxis of group A β-hemolytic streptococci infections with penicillin is the standard of care for all children diagnosed with SC regardless of chorea severity.

Anti-N-methyl-D-aspartic acid receptor encephalitis

Anti-NMDA receptor encephalitis is the prototypic antibody-mediated encephalitis associated with chorea in childhood. The clinical presentation is quite classical with subacute onset of seizures, dyskinesias, insomnia, psychiatric symptoms, and autonomic instability. The clinical awareness of the disease in the last decade led to a noteworthy increase in the number of patients diagnosed with this clinical entity. Etiology-specific treatment of anti-NMDA receptor encephalitis includes the surgical removal of the tumor if present (most commonly ovarian teratomas) and several types of immunomodulatory treatments either alone or in combination including steroids, IVIG, PLEX, rituximab, and cyclophosphamide.[123,124]

Antiphospholipid antibody syndrome and systemic lupus erythematosus

Chorea is the most common movement disorder in patients with APS and SLE, and it may even be the initial presenting symptom. APS is either a primary or a secondary systemic autoimmune condition characterized by hypercoagulable state, which results in arterial and venous thrombosis and pregnancy morbidities. Anticoagulant or antiplatelet agents are the first step for chorea treatment in APS. For patients who do not respond, additional therapeutic options such as azothioprine, cyclophosphamide, IVIG, PLEX, and rituximab are reported.[125,126]

SLE is the most common secondary cause of APS, and the presence of antiphospholipid antibodies in SLE is defined as a strong risk factor for the development of chorea. Antiplatelet agents may be considered in patients with SLE with antiphospholipid antibodies. Chorea usually resolves with symptomatic therapy, and immunosuppressive agents may be considered in systemic disease activity.[125-127]

Moyamoya disease

Moyamoya disease is a progressive occlusive disease in which 3% of affected children may present with chorea. Although resolution may take months and relapses may occur, revascularization surgery has been reported to result in improvement of chorea.[4,128]

Conclusion

Currently available options for treating childhood chorea are many but often result in less-than-complete benefit. The large number of etiologies, the complex pathophysiology, and the presence of off-target effects for most available medications contribute to the therapeutic challenges. Even with increasing knowledge about underlying etiologies for chorea, the therapeutic approach requires complex clinical reasoning that relies on knowledge of neurochemistry, neural circuitry, immunologic mechanisms, and the natural history of the disorders. With a rational and systematic approach, prioritizing treatment of chorea that causes disability, meaningful clinical benefit can often be achieved even if chorea cannot be eliminated. In the future, it is expected that more etiology-based treatments will become available as the mechanisms are understood better.

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