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J Child Neurol 2003 18: S9 originally published online 1 January 2003
DOI: 10.1177/0883073803180010401

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Pathophysiology of Pediatric Movement Disorders

Terence D. Sanger, MD, PhD

ABSTRACT

Pediatric movement disorders constitute a relatively small cluster of symptoms that can be associated with many different underlying diseases. To provide effective treatment, it is essential to understand the relationship between etiology and clinical expression. This article reviews the recent literature on several common pediatric movement disorders, including spasticity, dystonia, chorea, myoclonus, bradykinesia, and tics, and it discusses current models of physiology that may help link the cellular pathology of specific diseases to the expression of clinical symptoms. (J Child Neurol 2003;18:S9–S24).

Movement disorders in childhood are symptoms of an underlying static or progressive disease process. This situation differs significantly from the nomenclature for adult movement disorders, in which the disease (eg, Parkinson’s disease) and the symptoms (eg, parkinsonism) often share a common name. Certainly, disorders such as Oppenheim’s dystonia are often considered to be “primary” disorders, but the discovery of multiple genetic causes for dystonia suggests that diagnosis and treatment may be better served by separating the symptoms from their causes.

The present review seeks to accomplish this separation by considering movement disorders as symptoms independent of their etiology. The goal is to progress toward understanding the link between the underlying cellular or molecular pathology and the clinical expression. The ultimate goal is to discover treatments or cures for childhood movement disorders. Treatment can be roughly divided into “etiologic” or “symptomatic,” in which etiologic treatment targets the arrest or reversal of the cellular or biochemical abnormalities that lead to the disease, whereas symptomatic treatment attempts to interrupt the physiologic mechanisms that lead to expression of clinical symptoms. Discovery of etiologic treatments will depend on research into the specific causes of each disease, and most diseases will yield only to treatments designed to target their unique pathophysiologic processes. However, discovery of symptomatic treatments may benefit from the fact that multiple diseases may share a common clinical expression, so that research into the commonalities of these diseases can further the understanding of treatment for multiple different pathologies.

Symptomatic treatment depends on understanding the process by which a cellular or biochemical abnormality can lead to changes in behavior and therefore requires an understanding of both normal and abnormal brain function at multiple levels. Translation of behavior at one level (such as the cellular or molecular level) into behavior at another level (such as the systems or behavioral level) requires the use of models that are able to describe emergent properties of populations of functioning (or malfunctioning) cells.

In both child and adult neurology, the anatomic localization of injury is often highly predictive of the specific symptoms that emerge. For example, in adult neurology, specific symptoms or symptom complexes can be used to predict the location of lesions, such as strokes or tumors. In child neurology, anatomic localization is more often concentrated on a specific cell type rather than a localized region of brain. This is attributable to the relatively higher incidence of genetic or biochemical disorders that demonstrate expression only in particular cell subtypes. Therefore, in children, the expression of movement disorders is often linked to the failure of entire brain systems (such as the corticospinal tract, cerebellum, basal ganglia, thalamus, or hippocampus) or cell types (such as oligodendrocytes, cerebellar Purkinje cells, or cholinergic interneurons) rather than the dysfunction of localized regions. On the other hand, the developing brain appears to be relatively resilient to localized injury, so that after recovery, a large stroke that would be devastating to an adult may lead to only minimal symptoms in a child. Figure 1 shows a simplified diagram of
some of these motor systems; this article explores injury to individual systems in the following discussion.

In this review, discussion is confined to movement disorders in the following symptomatic groups: spasticity, dystonia, bradykinesia, chorea, ataxia, tics, myoclonus, tremor, hypotonia, and psychogenic disorders. Choreoathetosis is discussed under the “dystonia” category because these two symptoms frequently coexist and may represent variants of the same disorder. The pathophysiology for some of these disorders has been extensively reviewed elsewhere; here discussion is confined to particular issues relating the pathophysiology to the clinical symptoms.

**SPASTICITY**

The Taskforce on Childhood Motor Disorders defines spasticity as “hypertonia in which one or both of the following signs are present:

1. Resistance to externally imposed movement increases with increasing speed of stretch and varies with the direction of joint movement;
2. Resistance to externally imposed movement rises rapidly above a threshold speed or joint angle.”

Because spasticity is frequently associated with other symptoms, such as weakness, poorly differentiated control, clonus, muscle and tendon shortening, or joint contractures, it may be difficult to determine the extent to which spasticity per se is contributing to the disorder of movement. The spinal mechanisms of spasticity have been extensively reviewed elsewhere and are not discussed here.

By definition, spasticity is a clinically observable phenomenon that responds predictably to manipulation. In particular, the reactive force generated by a spastic muscle depends on the speed and direction of passive movement. The low latency of the response suggests spinal mechanisms, and extensive investigation has shown that spasticity is associated with increased excitability of spinal motoneuron pools. Although in some cases of severe spasticity, the heightened reflexes can lead to disability (eg, if stepping activates a reflex contraction in the ankle extensors or if the reflexes are engaged at rest with continuous muscle activation), it is not clear whether spasticity itself is a common cause of disability or merely an associated clinical sign. The spinal mechanisms of spasticity have been extensively reviewed elsewhere and are not discussed here.

Figure 1. Illustrations of some of the major motor systems and pathways controlling limb movement. The diagram is for illustration only; the actual systems and interconnections are considerably more complex. GPe = internal globus pallidus; STN = subthalamic nucleus.
ticy can result from injury at many sites along the pathway that connects the primary motor and premotor cortex to spinal circuitry.\textsuperscript{19,23} It is equally clear that many other sites of injury (including lesions of the cerebellum, basal ganglia, temporal lobes, and sensory pathways) do not commonly lead to spasticity. Proceeding from distal to proximal, lesions that can cause spasticity can be located

1. in the descending spinal tracts, as is frequently seen in spinal cord injury
2. in the midbrain or pons, although pediatric lesions in this region are often fatal
3. in the internal capsule, as may occur with stroke
4. in the periventricular white matter, as is frequently seen in prematurity
5. in the motor or premotor cortex, as may occur with stroke

In theory, a lesion that results in decreased input excitation to the motor cortex or excessive inhibition of the motor cortex could produce symptoms similar to a lesion, although no conclusive evidence has been shown for this mechanism. Whether decreased signaling in descending pathways is sufficient for the development of spasticity or whether there must actually be loss of presynaptic nerve terminals is not known.

The many possible causes of lesions at each of the possible locations are not discussed here. However, it is important to realize that central white-matter lesions are a very frequent contributor to spasticity in children. The reason for this is likely to be the relative sensitivity of oligodendrocyte precursors to hypoxic or ischemic injury during the early part of the third trimester of pregnancy and the resulting higher incidence owing to prematurity.\textsuperscript{24} Another reason is the predilection of some childhood-onset neurodegenerative diseases for destruction of central white matter (including X-linked adrenoleukodystrophy, metachromatic leukodystrophy, Pelizaeus-Merzbacher disease, and others).

The manifestation of spasticity owing to central white-matter or cortical injury may be different from the manifestation of spasticity owing to spinal injury. In particular, injury above the level of the brain stem leads to interruption of corticobulbar connections (between the cerebral cortex and brain stem), with preservation of bulbospinal connections (between the brain stem and spinal cord; see Figure 1). This may remove the origins of the vestibulospinal, rubrospinal, and reticulospinal tracts from cortical control, and some authors have suggested that disinhibition of the neurons contributing to the noncorticospinal tracts is a primary cause of lower extremity tonic extensor posturing in children with severe periventricular leukomalacia.\textsuperscript{17,19} The disinhibited vestibulospinal tract may be responsible for the dramatic changes in tone that often occur with repositioning. Because one postulated role of the vestibulospinal tract may be the maintenance of “antigravity” muscles, it may be responsible for the “pyramidal distribution” of increased tone in which the leg extensor muscles show greater spasticity than the leg flexors and the arm flexor muscles show greater spasticity than the arm extensors.\textsuperscript{25}

The role of other descending tracts in contributing to spasticity is less clear, although dysfunction is likely to account for many of the associated deficits. In particular, loss of control of the rubrospinal tract may be responsible for decreased fine motor control, loss of flexor tone, and loss of individuation of flexor or extensor muscles.\textsuperscript{26} Loss of inhibition of the reticulospinal tract may be responsible for the increased auditory startle response often seen in premature children.\textsuperscript{27} On the other hand, preservation of descending autonomic control means that children with central white-matter or cortical injury do not suffer the severe autonomic instability that occurs in spinal cord injury. In unilateral hemispheric injury (such as in congenital hemispheric stroke), bilateral innervation of brainstem structures from the surviving hemicortex may be a primary mechanism for recovery of bilateral movement. Therefore, it remains critically important to distinguish injury above the level of the brain stem from injury to the spinal cord because the clinical course, symptoms, and prognosis will be very different in these two cases.

 Interruption of corticospinal tract fibers would be expected to occur in both central white-matter and spinal injury, although the role of this tract in humans remains
controversial. It is likely that direct projections of corticospinal axons to spinal motoneurons contribute to the ability for fine dexterous manipulation, and the primary effect of injury to these projections may be loss of dexterity in hand function. However, animal data suggest that destruction of the corticospinal tract is unable to replicate clinical features of spasticity, some primates (and most nonprimates) do not have direct corticospinal tract projections to spinal motoneurons, and interspecies comparisons have raised doubts about the relationship of this tract to manual dexterity.

The evolution of spasticity is interesting and may provide some clues to etiology and possibilities for intervention. Following spinal cord injury, there is an initial period of flaccid paralysis that is followed by a gradual increase in reflexes (often unaccompanied by a severe increase in hypertonia). Following hypoxic-ischemic injury, there is a longer period of hypotonia, often lasting several months, that is gradually replaced by spasticity within the first years of life. It is tempting to speculate that the gradual onset of spasticity represents a gradual compensatory increase in the excitability of spinal motoneuron pools in response to decreased descending cortical input. (Certainly, there are other long-term effects, including muscle and tendon shortening and joint contractures that contribute to hypertonia and eventual disability.) However, in cases of incomplete injury, there may be partial recovery of descending signals. If this recovery occurs more slowly than the increase in spinal excitability, the cortex may find itself trying to regain control of already spastic muscles. This would suggest that if spasticity were able to be prevented during the early recovery phase from injury (using medication or aggressive physical therapy) or if descending signals were to be increased (using active attempts at movement, including supported walking or biofeedback), then it might be possible to reduce the increase in spinal excitability to the minimal level needed to compensate for the recovering descending signals.

Hypertonia is an increased resistance to passive stretch while a subject is attempting to maintain relaxation. Spasticity is an important cause of hypertonia, but increased tone may also be attributable to passive tissue properties (the force generated by electrically silent muscle) or the inability to relax the muscle prior to the start of the passive movement. The interaction of different causes of hypertonia can be illustrated by considering Hill’s “active state” model of force versus length for muscle activation, which is shown schematically in Figure 3 (a similar figure could be constructed for force versus velocity). The lowest line in the figure indicates the relationship between applied force and position for an electrically silent muscle. The rise in force toward full stretch of the muscle is attributable to viscoelastic properties of the relaxed muscle fibers as they are stretched beyond their normal length. The uppermost line represents the relationship between force and length when the muscle is fully activated via tetanic stimulation. As drawn in the (simulated) figure, this line is the sum of the force generated by initially active fibers, reflex activation, and voluntary force. The dotted line shows the sum of all the involuntary components of force (solid line, which includes reflex and initial background activation) and the maximal force generated by the muscle (the fully active state).

Figure 3. Simulated applied force for each position of a joint during passive movement. Activation of reflex muscle activity leads to a rise in force (solid line) from the force generated by the initially active fibers (dot-dash) toward the fully active state (dot-dot). This occurs at joint position R1. R2 is the position where the passive properties of the fibers (dash-dash) lead to increasing resistance as they are stretched to their maximal length. The maximal voluntary force at each position (gray region) is the difference between the involuntary components of force (solid line, which includes reflex and initial background activation) and the maximal force generated by the muscle (the fully active state).

Although Figure 3 is only a schematic illustration, it indicates the way in which the mechanical properties of relaxed or contracting muscle contribute to hypertonia. Because voluntary force is the difference between maximally activated muscle and the force generated involuntarily (prior to voluntary activation), the height of the gray region in Figure 3 is the upper bound on the amount of obtainable voluntary force at each position of the joint. This shows one way in which an increase in baseline tone can contribute to weakness. (Note that there are many other causes of weakness, including activity in antagonist muscles or inability to generate an adequate stimulus to the muscle.) Normal muscle is silent at rest, so electro-
Dystonia

The Taskforce on Childhood Motor Disorders defines dystonia as “a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both.”1 Dystonia is probably underreported in children with movement disorders. Although at least 10% of cerebral palsy is primarily dyskinetic (which includes dystonia),38–43 it is likely that many children with a primarily spastic clinical picture also have some degree of dystonia. In particular, dystonia often affects the arms of children with tetraplegic cerebral palsy and may be commonly seen in the arm or hand of children with congenital hemiplegia. This is very likely attributable to hypoxic-ischemic injury to neurons in the basal ganglia, often caused by severe injury in term neonates. Dystonia is also a common feature of metabolic or neurodegenerative diseases, particularly those affecting the basal ganglia (eg, dopa-responsive dystonia, primary dystonia, pantothenate kinase 2 deficiency [Hallervorden-Spatz disease], and glutaric aciduria type I). Dystonic hand or arm posturing is frequently seen in choreothetobrbral palsy, and the worsening of athetotic movements with attempted voluntary movement suggests that this disorder may be more closely related to dystonia than to chorea or athetosis. I hypothesize that many children with a diagnosis of “choreothetosis” actually have a form of hyperkinetic dystonia, in which involuntary but nonsimultaneous activation of agonist and antagonist muscles can lead to wild flailing of the limbs. In contrast, dystonia causes hypertonia (without choreothetosis) when there is simultaneous co-contraction of agonist and antagonist muscles at rest, so that attempts at muscle stretch meet with immediate resistance from an already contracting muscle.1

The dot-dash line in Figure 3 shows a simulation of increased tone as a result of initially contracting muscle fibers, as would be expected in dystonia.

The anatomic localization of dystonia is most often thought to be in the basal ganglia, in particular with injury to the caudate, putamen, or sensory thalamus.44–49 Magnetic resonance imaging evidence of injury to the basal ganglia or thalamus at the time of birth is predictive of later onset of dyskinetic cerebral palsy.49,60,61 However, diseases such as dopa-responsive dystonia suggest that primary deficiency of dopamine-synthesizing cells in the substantia nigra pars compacta can be a cause, and adult-onset focal task–specific dystonia may be related to sensory cortical dysfunction41–47 or thalamic dysfunction.58,59 There are animal models suggesting that cerebellar dysfunction may also lead to dystonia.60,61 Therefore, the anatomic localization of a lesion causing dystonic symptoms may be difficult to establish without taking into account other findings.

Despite the difficulty in localization, the presence of dystonia does indicate injury above the level of corticospinal and corticobulbar projections, in the sense that the basal ganglia outputs modulate cortical activity; therefore, basal ganglia injury can be expressed only when signals pass through a relatively more intact cortex. From a clinical point of view, this means that dystonia is a central disorder associated with attempted voluntary movement. It is relatively insensitive to passive manipulation of the limbs. For example, the velocity-dependent tone seen in spasticity is generally not observed in dystonia because when dystonia produces increased tone, this is usually attributable to co-contraction at baseline that precedes clinical attempts at passive movement.1 The result of dystonia is an abnormal spatial or temporal pattern of muscle activity associated with intended movement. The abnormal spatial pattern can lead to co-contraction or “overflow” of movements to ordinarily uninvolved muscles or limbs,59 whereas the abnormal temporal pattern can lead to dyskinetic or ballistic movements of muscles that become active earlier or later than intended. Unlike spasticity, dystonia is probably not a compensatory mechanism and is always detrimental to motor function.

Overflow movements may be a specific dysfunction related to a recent model of normal basal ganglia function. It has been hypothesized that one purpose of the basal ganglia is to focus cortical activity to select desired actions while suppressing similar movements that are not desired.59 Therefore, one might imagine that dysfunction of the basal ganglia could lead to lack of this focusing operation or even an inversion of the focusing operation, such that desired movements are inhibited, whereas undesired ones are accentuated. Certainly, one might guess that any reduction in focusing could cause a spread of activity to muscles unrelated to the required task.

Electrophysiologic correlates of dystonia are seen at the muscular, central motor, and central sensory levels. In particular, EMG recordings show increased tonic activity in muscles that are normally uninvolved in a movement, and there may be high-amplitude synchronous rhythmic bursting discharges.59,63,64 Imaging studies show activity occurring over large areas of motor regions of the cortex.54 Electrophysiologic recording during surgery shows cells in the basal ganglia and thalamus with very large sensory receptive fields that can extend over an entire side of the body; in some cases, they have bilateral sensory receptive fields.60,61 The spread of sensory and motor activity is probably related to the overflow of muscle activity, but whether the central changes

myographic (EMG) activity during attempted relaxation is abnormal and may be attributable either to activation of spinal reflex circuits or involuntary descending signals from supraspinal regions.

When spasticity is present, there is a rapid rise in applied force when the velocity of movement exceeds a threshold. In this case, the joint position at which the rapid rise in force occurs can be measured (R1) and compared with the maximum obtainable joint position with very slow movement (R2). Measurement of R1 and R2 is the central component of the Tardieu scale of spasticity.37 Other important measures include the average amount of force required to move the joint or the work required (integral of the force versus position curve). The slope of the force versus position curve at each point gives the stiffness, and even in the absence of a spastic catch, there may be increased stiffness owing to initially active muscle fibers.
cause or result from the dystonic movements has not yet been determined.

When dystonia is caused by basal ganglia dysfunction, there is evidence that it may be attributable to a failure in dopaminergic transmission.\textsuperscript{65,66} In particular, dystonia can be caused by medications that block dopamine receptors (such as neuroleptics),\textsuperscript{67} diseases that reduce dopamine production (such as dopa-responsive dystonia),\textsuperscript{68–70} and diseases that destroy the medium spiny cells that are the targets of dopamine (such as Huntington’s disease).\textsuperscript{71–73} In humans, medications that produce combined D\textsubscript{1} and D\textsubscript{2} inhibition (such as tetrabenazine) do not produce dystonia, whereas selective D\textsubscript{2} antagonists (such as haloperidol) do.\textsuperscript{74–76}

The relationship between dysfunction of dopaminergic transmission and the symptoms of dystonia is not known. Understanding this relationship will require an understanding of the basal ganglia circuitry. The current model of basal ganglia circuitry is described by two pathways that loop from the cortex through the striatum, pallidum, and thalamus and back to the cortex (this topic has been extensively reviewed elsewhere\textsuperscript{77–79} and is described here only briefly). Figure 4 shows an illustration of the overall structure. These pathways are distinguished not only by their anatomic connections but also by the type of dopamine receptors on the medium spiny cells in the striatum. The “direct” pathway has an even number of inhibitory \( \gamma \)-aminobutyric (GABA)-ergic synapses and goes through medium spiny cells with primarily D\textsubscript{1}-like receptors, whereas the “indirect” pathway has an odd number of GABA-ergic synapses and goes through medium spiny cells with primarily D\textsubscript{2}-like receptors. Classically, the differing number of inhibitory synapses has been taken to imply that the direct pathway has a net excitatory effect on cortex, whereas the indirect pathway has a net inhibitory effect.

Unfortunately, the assumption of inhibitory effects of the indirect pathway appears to be at odds with clinical experience that suggests an association of dystonia with excessive activity in the indirect pathway. A recent computational model by this author suggests an alternate interpretation in which the direct pathway is a positive feedback loop, whereas the indirect pathway is a negative feedback loop. The importance of this distinction is that both positive and negative feedback loops can become unstable if the gain (the increase in the signal as it travels around the loop) is sufficiently high. If dystonia is the clinical manifestation of instability and saturation in the basal ganglia loop, then disinhibition of the indirect pathway could be a cause of instability and thereby dystonia. Because D\textsubscript{2}-like receptors are inhibitory, blockade of D\textsubscript{2}-like receptors (by neuroleptic medications) would result in indirect pathway disinhibition and increased potential for dystonia. Conversely, stimulation of D\textsubscript{1}-like receptors (by dopamine) would inhibit the indirect pathway and reduce dystonia. Any intervention that reduces the gain in an unstable basal ganglia loop could be helpful for treating dystonia, so a surgical lesion or deep brain electrode in the internal globus pallidus or thalamus might be effective by reducing the magnitude of the basal ganglia outflow to cortex.

Anticholinergic medication has traditionally been one of the most effective medications for controlling childhood dystonia of all types, although its mechanism of action is poorly understood.\textsuperscript{80–85} Acetylcholine is prevalent in many brain regions, but the relationship to dystonia may be attributable to the large aspiny cholinergic cells in the striatum. These cells interact with D\textsubscript{1}-bearing medium spiny neurons through M\textsubscript{2}-type cholinergic receptors and with D\textsubscript{2}-bearing medium spiny neurons through M\textsubscript{3}-type cholinergic receptors.\textsuperscript{86–88} Because M\textsubscript{1} receptors are primarily depolarizing, whereas M\textsubscript{3} receptors are primarily hyperpolarizing, the differential effect of acetylcholine on D\textsubscript{1}-bearing and D\textsubscript{2}-bearing medium spiny neurons would be expected to be the opposite of the effect of dopamine.\textsuperscript{89} The situation is certainly more complicated than this because the large aspiny neurons possess synapses with both pre- and postsynaptic D\textsubscript{2}-like receptors, and there is evidence of a reciprocal connection from D\textsubscript{1}-bearing medium spiny neurons back to the large aspiny cholinergic interneurons. However, the simplest explanation of function based on current knowledge would be that blockade of cholinergic transmission would be expected to have some of the effects of stimulation of dopaminergic transmission, and this may explain the benefit in both parkinsonian symptoms and some cases of dystonia.

One puzzling feature of the origin and treatment of dystonia is the very slow development or resolution of symptoms following either injury or surgical intervention.\textsuperscript{90–92} In particular, dystonia can appear or worsen in children many years following a presumably static hypoxic injury to basal ganglia, and it may continue to improve for up to 1 year after pallidotomy or deep brain electrode implantation.\textsuperscript{93–97} Although it is possible that some cases of delayed-onset
dystonia represent ongoing neuronal injury, the nearly complete resolution of symptoms after many years, as is seen in dopa-responsive dystonia, suggests that progressive injury is not a necessary feature. It is possible that there is a threshold effect with aging, such that increasing demands on the motor system lead to expression of symptoms, but the fact that symptoms can have rapid onset over a few months after up to 12 years of normal development makes this unlikely.

Another intriguing hypothesis is that synaptic plasticity mechanisms are responsible for the gradual onset of symptoms. Both long-term potentiation and long-term depression are known to occur at corticostriatal glutamatergic synapses, and long-term potentiation and long-term depression at these synapses are modulated by dopamine, as well as presynaptic and postsynaptic activity.96–103 Certainly, a prolonged failure of dopaminergic transmission might be expected to lead to abnormal patterns of long-term potentiation and long-term depression, which could contribute to abnormal patterns of muscle activity in dystonia. In addition, continued abnormal motor patterns could potentially reinforce themselves at intracortical, thalamocortical, or corticostriatal synapses, so that the persistence of symptoms is attributable to a “vicious cycle” of perpetually self-reinforcing dystonic muscle patterns. Any improvement would occur gradually as synapses readjust to more normal patterns of movement. Whether movement practice or physical therapy could be helpful in retraining movements in this context is a matter of speculation.

RIGIDITY AND BRADYKINESIA

The Taskforce on Childhood Motor Disorders defines rigidity as hypertonia in which all of the following are true:

1. The resistance to externally imposed joint movement is present at very low speeds of movement, does not depend on imposed speed, and does not exhibit a speed or angle threshold.
2. Simultaneous co-contraction of agonists and antagonists may occur, and this is reflected in an immediate resistance to a reversal of the direction of movement about a joint.
3. The limb does not tend to return toward a particular fixed posture or extreme joint angle.
4. Voluntary activity in distant muscle groups does not lead to involuntary movements about the rigid joints, although rigidity may worsen.

In children, rigidity is unusual and occurs as the expression of rare diseases associated with primary failure of dopamine production. In juvenile Parkinson’s disease, the dopamine-producing neurons of the substantia nigra are lost.104–106 In dopa-responsive dystonia (most commonly owing to guanosine triphosphate–cytidylyltransferase deficiency or tyrosine hydroxylase deficiency), the neurons are intact but are unable to synthesize dopamine.68,69 Both of these diseases can present with a mixed parkinsonian and dystonic syndrome. Both diseases improve with dopaminergic medication. In addition, parkinsonism can be produced by tetrabenazine, a medication that blocks release of dopamine at synapses independent of receptor subtype.107–110 The occurrence of rigidity in other childhood disorders, including cerebral palsy, is difficult to determine owing to a lack of a standard method for measurement.

Parkinsonian tremor is rare in children, so the usual manifestations of parkinsonism include a combination of rigidity and bradykinesia. Bradykinesia is a slowness of initiation and execution of voluntary movement, although reaction time and the speed of complex reflexive movements may be preserved (eg, a child or adult with parkinsonism may be able to catch a ball but not throw it).111,112 Like dystonia, bradykinesia represents a centrally mediated abnormality of voluntary movement. Rigidity, however, is sensitive to passive manipulation, and, in fact, the EMG may be silent at rest and active only in the muscle that opposes passive movement. Bradykinesia is probably not attributable to antagonist muscle activation but rather to inadequate activation of agonists.111–114 There is no velocity dependence, and rigidity tends to be equal in both flexion and extension. It is therefore likely that rigidity is not mediated by spinal mechanisms but may instead represent a cortically mediated resistance to passive movement, perhaps involving activation of long-loop transcortical reflexes.111,112

I have hypothesized that in children, parkinsonism and dystonia represent a continuum of abnormalities in the basal ganglia. Parkinsonism occurs when indirect pathway transmission is moderately increased relative to direct pathway transmission, so that the basal ganglia loop is inverting and serves to reduce the amplitude of any desired cortical pattern. Therefore, any attempt at movement that depends on a particular pattern of motor cortical activation leads immediately to a reduction in the cortical pattern. However, in parkinsonism, the overall gain remains stable, so that the unstable feedback loop described above for dystonia does not occur. With more severe increases in indirect transmission relative to direct transmission, the loop may become unstable, and dystonia could supervene. It is possible that a combination of dystonia and parkinsonism could coexist if some movement patterns are unstable, whereas others are merely inhibited.

Because the usual cause of bradykinesia and rigidity is a primary failure of dopaminergic synthesis or release, treatment with L-dopa is usually effective. However, prolonged treatment with L-dopa in juvenile Parkinson’s disease (but not in dopa-responsive dystonia) can lead to the development of severe and disabling dyskinesias.115,116 Deep brain electrodes or lesions placed in either the subthalamic nucleus or the internal globus pallidus can improve overall function in adults with Parkinson’s disease,117 but there is almost no experience with these treatments in children with parkinsonism. In adults, electrode placement in the internal globus pallidus reduces dyskinesias118 and may allow an increase in the tolerable dosage of L-dopa (and thus allow improvement in parkinsonian symptoms), whereas electrode placement in the subthalamic nucleus improves parkinsonian symptoms (and may allow a decrease in the dosage of L-dopa).119–121 The mechanism of internal globus pallidus lesion or electrode placement may be related to blocking abnormal signals, as
in dystonia. The mechanism of function with subthalamic nucleus placement may be a reduction in the excitatory drive to the internal globus pallidus, with consequent disinhibition of the pallidal targets in the thalamus and thereby increased thalamic drive of the cortex.

**CHOREA AND BALLISM**

Although many authors distinguish chorea and ballism based on the magnitude of the movement, the violent nature of the movement, or the involvement of proximal versus distal joints, I will consider both disorders to be variants of chorea. Unlike dystonia, chorea is a disorder that is worst at rest and may remain unchanged or improve with voluntary movement. It does not appear to involve stereotyped patterns of muscles; rather, it will move seemingly randomly from one body part to another. Unlike spasticity or rigidity, there is no disorder of tone, and reflexes are generally normal (as long as no other symptoms are involved).

Whereas chorea in adults is the result of either neurodegenerative disease (eg, Huntington's disease) or a lesion near the subthalamic nucleus, in children, chorea is most often associated with iatrogenic (eg, antiepilepsy medications), inflammatory (eg, Sydenham's chorea), infectious (eg, viral encephalitis), or structural (eg, holoprosencephaly) etiologies. There are few data on the pathophysiology of chorea in children, and extensive neuromaging studies of children with Sydenham's chorea have failed to indicate a clear relationship between this symptom and inflammation of the basal ganglia. In adults, studies of Huntington's chorea suggest that the choreatic presentation is associated with selective loss of D2-bearing medium spiny neurons in the striatum, and loss of these cells might be expected to lead to disinhibition of the external pallidum and thereby excess inhibition of the subthalamic nucleus (see Figure 1).

Therefore, the known mechanisms of chorea involve either destruction or inhibition of the subthalamic nucleus, but whether this is the only possible mechanism of generating chorea is unknown.

The subthalamic nucleus has glutamatergic projections directly from the motor and premotor cortex, so another potential mechanism for reduced subthalamic nucleus activity would be a lack of cortical excitatory drive. This could provide an additional potential mechanism for the development of chorea in encephalitis if destruction of the frontal cortex were involved. Of course, direct injection of cells of the subthalamic nucleus could also contribute, and the frequent involvement of extraocular movements suggests potential involvement of the adjacent substantia nigra pars reticulata. However, many presentations of chorea remain unresolved. For example, chorea is often an early and prominent symptom in ataxia-telangiectasia, yet the primary site of pathology in this disorder is thought to be located in the cerebellum.

Whatever the cause, one might hypothesize that decreased output from the subthalamic nucleus would result in decreased excitation of the internal globus pallidus. Because the pallidal outputs to thalamus are primarily inhibitory, the result would be decreased inhibition of thalamocortical projections and therefore a potential for increased cortical activity. However, this simple model does not explain the apparently random generation of recognizable movement fragments or the lack of hypertonia seen in chorea. Another hypothesis might be that one function of subthalamic nucleus output is to prevent the activation of movements by holding the internal pallidum in a relatively depolarized state. Initiation of normal movement at a particular time would then be associated with a transient and selective reduction of activity within the subthalamic nucleus that would release the “brake” on the internal pallidum and allow activity to flow uninterrupted through the basal ganglia loop from the cortex through the striatum, pallidum, and thalamus and back to the cortex. Destruction or inhibition of the subthalamic nucleus would effectively release this brake simultaneously on all possible movements, so that neither the time of initiation of movement nor the particular movement to be initiated could be selected. The basal ganglia might then nonselectively amplify ongoing low-level activity in the cortex, which might appear as random and unintended movement fragments.

**TICS**

Tic disorders are probably the most common movement disorder in children, yet they only rarely cause severe disability. Like chorea, the timing of occurrence of tics appears to be random, and they do not interfere with the performance of skilled movement (although they may interrupt a sequence of activities). It is possible that chorea and tics could both be caused by complications of streptococcal infection, although the prevalence and mechanism of this are unknown. Other than this situation, however, tics and chorea do not commonly occur together, and tics more often co-occur with obsessive-compulsive traits or attention-deficit hyperactivity disorder (ADHD). Also, unlike chorea, children with tics will often describe a distinct sensation that heralds the need to make the tic and that resolves on performing the movement. There is often a sense that the movement is voluntary but is made in response to an overwhelming and irresistible urge. By definition, tics are stereotyped, repetitive, and often complex movements, whereas chorea appears to be more random and unpredictable.

The mechanism of tics remains obscure. Tics will often respond to treatment with neuroleptic medication, suggesting that hyperactivity of the direct or hypoactivity of the indirect basal ganglia pathway could be a cause and that symptoms resolve when the indirect pathway is stimulated. However, the prevalence of D2-like receptors in cortical regions means that the mechanism of action of these medications in tics could be unrelated to their effect on basal ganglia. The selective serotonin reuptake inhibitors may also be effective for tic disorders, and whether this is attributable to a reduction of anxiety with a consequent reduction in triggers for tics, to the antidopaminergic effects of these medications, or to a direct effect on serotonin transmission is unknown.

Some children with tics may display suggestibility and, in extreme cases, echopraxia. There is a frequent association with ADHD in the same child or in family mem-
bers. Therefore, part of the mechanism may be associated with an inability to suppress voluntary movement. Echopraxia and inability to suppress movement also occur in adult dementias, particularly with frontal lobe or orbitofrontal region dysfunction. Whether this is related to the localization in children is unknown.

**MYOCLONUS**

Myoclonus is categorized by its expression as focal, segmental, or generalized and by its etiologic location as cortical, subcortical, propriospinal, or spinal. The EMG in myoclonus will often consist of bursts lasting less than 50 milliseconds. Such a pattern cannot be produced voluntarily.

In both children and adults, myoclonus is associated with destruction or irritation of cortical or subcortical gray matter. It occurs in inflammatory disorders (the presumed mechanism associated with neuroblastoma), neurodegenerative disorders (such as Tay-Sachs disease, neuronal ceroid lipofuscinosis, mitochondrial encephalomyopathies, subacute sclerosing panencephalitis, or dentatorubral-pallidoluysian atrophy), seizure syndromes (including infantile epileptiopathies and juvenile myoclonic epilepsy), encephalitis (such as acute encephalitis and Rasmussen’s encephalitis), severe hypoxic injury (such as with near-drowning), and focal mass lesions or dysplasias (often manifesting as epilepsy partialis continua).

Unlike in adults, in children, myoclonus is not a common manifestation of systemic metabolic derangement (such as hyperammonemia or hypercarbia). Therefore, when it occurs in children, myoclonus should lead to suspicion of a severe and potentially progressive disorder; thorough investigation of the cause is usually required.

The association of myoclonus with seizure disorders suggests that in many cases, these disorders may share a common general mechanism. In particular, it suggests that the primary disorder in myoclonus may be related to impaired regulation of neuronal excitability. This would be in contrast to many of the other disorders discussed here, in which the primary disorder is one of system-level dysfunction and for which changes in cellular excitability are secondary to changes in the nature or magnitude of signals within neural circuits.

Because effective treatment of myoclonus often involves the use of medication that potentiates transmission at GABA synapses (such as clonazepam or valproate), it is possible that in some cases, the mechanism involves a primary failure of inhibitory circuitry. However, it is also possible that an increased “irritability” of neurons can be partially compensated by increased inhibitory drive. In cortical myoclonus, there appears to be a direct relationship between firing of individual regions of cortex and the resulting EMG signals, suggesting that the abnormality is occurring in the output cells of the cortex (those driving descending corticospinal or corticobulbar tracts). In particular, averaging of electroencephalographic signals time-locked to myoclonic jerks (jerk-locked back-averaging) will often show a focal region of the cortex that appears to be associated with the movements. In some cases, giant somatosensory evoked potentials are present, suggesting combined involvement of sensory systems or a hyperexcitability of the cortex in response to input. In adults with myoclonus, a transcortical C reflex can sometimes be elicited, suggesting that the hyperexcitability allows sensory inputs to drive motor outputs in the absence of a voluntary command for movement.

Some cases of myoclonus respond to treatment with serotonergic agonists or selective serotonin reuptake inhibitors, whereas, on the other hand, myoclonus can be a feature of the serotonin syndrome with presumed hyperactivity of serotonergic systems. The differing effects of serotonin could potentially be attributable to different receptor subtypes, but the role of serotonin in myoclonus is not yet understood.

**TREMOR**

Rhythmic oscillating movements can be caused by dystonia or myoclonus, in which case, they are referred to as “dystonic tremor” or “myoclonic tremor.” Intention tremor occurs near the end point of a voluntary movement and is usually related to cerebellar dysfunction. It is essential to distinguish these forms of tremor to determine the correct etiology. Clues to dystonic tremor include an irregular rhythm, variation in involved muscle groups with different postures, or worsening with intended movement. Clues to myoclonic tremor can be provided if the EMG shows short bursts of activity less than 50 milliseconds. Clues to intentional or ataxic tremor include inaccurate movements, posture, or shaking-shuddering spells. Tremor is described in terms of its triggering movements and thus is categorized as “rest tremor,” “postural tremor,” “action tremor,” and “intention tremor.” Tremor may be action specific. The type of tremor often gives a clue to the anatomic localization.

When tremor owing to dystonia, myoclonus, or ataxia is eliminated, the remaining causes of tremor are rare in children. Juvenile Parkinson’s disease generally does not present with tremor initially, nor do other causes of childhood-onset parkinsonism. It is important to exclude Wilson’s disease as a cause of tremor, although this disorder is rare. Tremor is associated with medications, including antiepilepsy drugs, stimulants, and bronchodilators. Tremor is also associated with acute metabolic disturbances such as hypoglycemia and may be a symptom of rheumatologic disease. Tremor may be caused by injury to regions in the brain stem, particularly in the region of the red nucleus. Tremor owing to lesions in this area is often referred to as “rubral tremor” or “midbrain tremor” and is thought to be attributable to oscillations within the Guillain-Mollaret triangle involving a feedback loop between the deep cerebellar nuclei, red nucleus, and inferior olivary nucleus. When other causes are excluded, tremor is often assumed to be caused by early onset of essential tremor. Because this disease is usually familial, there may be clues to the diagnosis in the family history. Affected adult family members may describe improve-
ment with alcohol. In addition, the disorder may be suggested by the sensitivity of symptoms to particular postures.

The mechanism of essential tremor is thought to be related to feedback loops involving the cerebellum, brain stem, and cortex (Figure 5). In some adult patients, interruption of the thalamic relays in ventral intermediate nucleus conveying cerebellar outflow to the motor cortex can improve symptoms. Whether improvement with alcohol is attributable to a direct effect on cerebellar function is a matter of speculation. In adult experiments, the tremor frequency is often independent of the mechanical parameters of the limbs, implying that the tremor is generated by a central oscillator and does not involve feedback from the periphery. In some but not all cases, tremor involves relatively normal EMG patterns, with alternating activity of agonists and antagonists about a joint, suggesting that it has recruited high-level motor control structures that are being driven in a manner similar to how they would be activated by voluntary movement.

ATAXIA

Children with ataxia are observed to have poor limb coordination, poor target accuracy, and poor balance. From the point of view of biomechanics, these three phenomena have in common a reduced ability to compensate for the dynamic inertial properties of the body and limbs. For example, a smooth reaching movement of the arm requires that the elbow forces compensate for the acceleration and Coriolis (rotational) forces generated by shoulder extension. Accurate target contact requires muscle contraction to counteract the forward momentum of the arm and stop it at the desired location. Stable gait requires that foot placement and ground reaction forces compensate for inertia generated by movement of the hips, trunk, head, and arms. Intention tremor is thought to be attributable to inaccurate target contact, with consequent voluntary compensatory movements leading to overcorrection and oscillation near the target. Although this appears as a rhythmic oscillation and thus a type of tremor, the responsible mechanism is thought to be attributable to inaccuracy caused by cerebellar dysfunction; therefore, this is often best thought of as a feature of ataxia rather than a type of tremor.

Different regions of the cerebellum help with the coordination of different functions, and some localization is possible based on symptoms. In particular, involvement of the cerebellar vermis is often associated with gait disorders, whereas involvement of the flocculonodular lobe is associated with eye movement abnormalities. Hemispheric involvement tends to affect arm movements and may be seen most commonly on pointing tasks or rhythmic hand movements.

Ataxia suggests a localized disorder of the cerebellum, although it is often worst when the disorder is acute and may be relatively minimal in children with a congenital decrease in cerebellar size. Unlike the control of movement within single spinal segments and the local somatotopic organization of sensory and motor representations in the cortex, the cerebellum is in the unique position of being able to integrate sensory information from multiple spinal segments that receive information from proprioceptors throughout the body (see Figure 5). Connections between parallel fibers carrying information from disparate regions can be combined at synapses on a single Purkinje cell, and this information can be passed via the thalamus to the motor cortex to modify movement commands. Therefore, the cerebellum may be able to modify the motor command to a muscle based on the ongoing dynamics of the limb and the rest of the body. Such modification would be essential for smooth, accurate, and coordinated movement. Injury to the cerebellum might be expected to lead to the inability to modify muscle contraction to compensate for the dynamic forces generated by other body segments. In young children, cerebellar injury or malformation is often accompanied by generalized hypotonia, suggesting that part of the effect of cerebellar outflow to the cortex results in maintenance of baseline tone.

The cerebellum contains circuitry that may allow modification of synapses in response to errors in motor performance. In particular, the cerebellum receives inputs that can compare the desired response to movement with the actual measured response, and it may be able to use this information to modify selectively synapses within the cerebellar cortex or nuclei. It therefore may be an essential brain area for adaptation to changing or unknown mechanical environments. In children, it may be essential for allowing adaptation to changes in the child’s body size and mechanics during development.

Cerebellar disease may be static (such as in congenital malformations, cysts, or ataxic cerebral palsy), acute (such as in cerebellitis or medication toxicity), recurrent (such as in metabolic diseases with hyperammonemia), or pro-
gressive (such as in ataxia-telangiectasia, pontocerebellar hypoplasia, spinocerebellar ataxia, or congenital disorders of glycosylation). Most progressive cerebellar disorders are associated with neurodegenerative diseases that have other disabling manifestations. The clinical expression of ataxia will be similar for disorders that affect similar regions of the cerebellum. Ataxia is a negative motor symptom in the sense that it represents the lack of a necessary signal. There is no evidence that blockade of cerebellar outflow improves ataxia (unlike for the positive symptom of tremor, in which blockade of cerebellar outflow is often helpful).

**HYPOTONIA**

Technically, hypotonia is not a movement disorder, but it is often seen in young children with delayed motor development. Hypotonia may coexist with weakness, but it is important to distinguish these symptoms because the weakness is more likely to contribute to disability. Hypotonia is frequently seen in trunk and neck musculature, even in children in whom the limbs are hypertonic. The reason for this difference in distribution is not known.

Hypotonia indicates a decreased resistance to passive movement when the child is at rest, but it is possible that with active movement, the muscles are able to generate full force. The normal maintenance of tone is thought to be mediated by spinal stretch reflexes. (Because EMG is normally silent at rest, tone is probably not attributable to baseline co-contraction of muscles.) Therefore, decreased tone would indicate either decreased proprioceptive feedback, decreased spinal motoneuron function, or decreased linkage between the proprioceptive feedback and motoneuron output.

Appropriate levels of proprioceptive feedback depend on stretch receptor activation in spindle fibers. Receptor activation is determined by the active state of the muscle, the mechanical forces stretching the muscle, and the gamma motoneuron activity controlling intrinsic fiber length. Decreased proprioceptive feedback could thus be attributable to inadequate muscle contraction (associated with weakness as in spinal muscular atrophy), decreased stretch on the muscle (owing to tendon laxity or joint instability), or decreased intrinsic fiber activation (owing to an abnormal central or spinal drive to gamma motoneurons). Because hypotonia is frequently seen in infants with cerebellar ataxia, one might speculate that the cerebellum in some way modulates gamma motoneuron activation or monosynaptic stretch reflexes, but this has not been proven. The central regulation of polysynaptic spinal stretch reflexes is poorly understood.

**PSYCHOGENIC DISORDERS**

Although psychogenic movement disorders must remain a diagnosis of exclusion, the relative lack of medical sophistication in younger children can make these disorders easier to recognize than in adults. Unfortunately, psychogenic disorders often are symptoms of severe underlying psychopathology; therefore, treatment may remain frustrating.

Psychogenic disorders are usually not associated with degenerative or metabolic disease, mass lesions, or infections, inflammatory, or other etiologies requiring urgent treatment (although any recent, worsening, or otherwise unexplained psychiatric phenomena may require a neurologic work-up). However, psychogenic movement disorders may be the non-verbal expression of a psychiatric disorder that could lead to suicide, so prompt evaluation is essential.

The pathophysiology of psychogenic disorders can be interpreted in much the same way as other movement disorders. In particular, the drive to the frontal cortical motor system is determined by cognitive and emotional factors whose localization is most probably in prefrontal and orbitofrontal cortex and limbic areas. The high-level nature of the movement is usually associated with patterns of EMG consistent with voluntary movement and patterns of muscle activity that are readily reproducible voluntarily. In some adult studies, a Bereitschafts potential was associated with psychogenic movement, suggesting a normal pre-movement planning phase. However, unless the child is malingering, he or she may not be able to control the movement, and it may be disturbing or disabling.

Although very little is known about the physiology underlying psychogenic disorders, one may speculate that control of high-level behavior may use similar circuits through the basal ganglia as are used for low-level motor behavior. In particular, the selection of particular behaviors and the inhibition of undesired behavior may be regulated by mechanisms similar to those involved with selection of simpler components of movement. This could explain why some medications (such as neuroleptics) that are used to treat psychiatric disorders leading to psychogenic movement disorders may also be useful in nonpsychogenic movement disorders. A better understanding of the relationship between psychiatric disorders, psychogenic movement disorders, and basal ganglia function might be expected to lead to better treatments for these very difficult symptoms.

**WEAKNESS AND NEGATIVE SYMPTOMS**

Movement disorders can be separated into those that contribute excess motor activity (hypertonia, spasticity, dystonia, chorea, myoclonus, tics, tremor) and those that reduce motor activity or skill (hypotonia, ataxia, apraxia, bradykinesia, weakness, poorly differentiated muscle control). By analogy with psychiatric terminology, excess motor activity is a “positive” symptom, whereas decreased activity or skill is a “negative” symptom. Negative symptoms can be equally or more severely disabling than positive symptoms, and throughout the above text, we have indicated when such symptoms may coexist. Of particular importance is the coexistence of weakness with other disorders. Weakness may be very difficult to recognize when positive symptoms are also present, yet, as discussed above in the section on spasticity, weakness may be a more disabling feature. Weakness implies a decrease in ability to generate force voluntarily. It may be unrelated to the state of baseline muscle contraction. For example, a severely hypotonic child may have normal vol-
untary strength, whereas a child with severe hypertonia owing to spasticity may have no ability to generate any voluntary force. A child with dystonia may be weak if any attempted contraction of an agonist leads to co-contraction of the antagonist with minimal resultant net force.

Weakness can be attributable to pathology at almost any level of the motor system, including muscles, motor nerves, motoneurons, spinal cord, brain stem, or cortex. Weakness is not usually associated with cerebellar or basal ganglia pathology (unless another pathology is simultaneously present). Apparent weakness may be attributable to neglect if there are sensory or sensory processing deficits.24 In particular, because strength can be increased through the use of sensory feedback, it is possible that partial removal of feedback could reduce strength.22,23 Determining the localization of weakness can be very important in determining the diagnosis and prognosis.

CONCLUSION

The National Center for Medical Rehabilitation Research classifies manifestations of childhood disease into five levels: pathophysiology, impairment, disability, functional limitation, and societal limitation.27 By describing childhood movement disorders as symptoms of underlying disease, I have classified them at the level of impairment. The purpose of this review was to describe the current state of knowledge that links the pathophysiology of movement disorders to the resulting clinical impairments. Whereas definitive treatment of these disorders will require interruption of the underlying pathophysiologic process, symptomatic treatment can be accomplished by understanding and blocking the process that allows the pathophysiology to lead to impairment. Therefore, in the discussion above, I have sought to give examples of mechanisms by which pathology at the cellular or biochemical level could lead to the clinical expression of symptoms.

This approach attempts to link only the first two levels of the National Center for Medical Rehabilitation Research classification. Improvement for affected children may also be obtained by interrupting the process by which impairment leads to disability (often accomplished through therapy and assistive devices), disability leads to functional limitation (often accomplished by adaptive environments), and functional limitation leads to societal limitation (often accomplished by political and societal reform). The goal of biologic research and medical intervention is to arrest the cause and block the effect of movement disorders at their most basic levels of expression.

References


