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Current and emerging strategies for treatment of childhood dystonia

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ABSTRACT

Childhood dystonia is a movement disorder characterized by involuntary sustained or intermittent muscle contractions causing twisting and repetitive movements, abnormal postures, or both (Sanger et al, 2003). Dystonia is a devastating neurological condition that prevents the acquisition of normal motor skills during critical periods of development in children. Moreover, it is particularly debilitating in children when dystonia affects the upper extremities such that learning and consolidation of common daily motor actions are impeded. Thus, the treatment and rehabilitation of dystonia is a challenge that continuously requires exploration of novel interventions. This review will initially describe the underlying neurophysiological mechanisms of the motor impairments found in childhood dystonia followed by the clinical measurement tools that are available to document the presence and severity of symptoms. Finally, we will discuss the state-of-the-art of therapeutic options for childhood dystonia, with particular emphasis on emergent and innovative strategies.

Introduction

Childhood dystonia can lead to lifelong disability, thus it represents a significant health care and rehabilitation challenge. Currently, dyskinetic cerebral palsy (CP), a type of CP primarily associated with damage to the basal ganglia,[1] is the most common cause of dystonia in children. It accounts for approximately 10–15% of cases of cerebral palsy.[2,3] It has a total incidence of 0.15–0.25 per 1000 in Western countries with an expected prevalence in the US of 50,000–75,000.[4] Dystonia in children manifests differently than in adults, partly because childhood dystonia is a dynamic disorder that prevents the acquisition of typical motor skills during critical periods of learning and skill development.[5,6] This is particularly trying when dystonia affects the upper extremities, as when common motor actions associated with self-care and play are profoundly limited and when there are harmful consequences for school participation and social interaction.

It is important that the outcome measures chosen for this population clearly assess the symptoms of dystonia and the associated function. Sensitive outcome measures not only support the benefit of medical and rehabilitation intervention, but they allow for the comparison of different treatment options. Given the influence of dystonia on everyday life and the ongoing search for effective treatments, the use of targeted outcome measures is crucial.

Current intervention options, including physical and occupational therapies, pharmacological approaches, and deep brain stimulation, are often not successful or only partially successful in controlling symptoms.[7–9] As a result, there is a need to investigate new non-invasive options for treating dystonia in children.

The purpose of this paper is to describe the pathophysiology of childhood dystonia, review the clinical measures used to assess severity and motor impairments, and describe the state-of-the-art for therapeutic interventions.

Definition

A National Institutes of Health task force on childhood motor disorders established the following consensus-based definition of dystonia: "A movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both."[5] The etymology of dystonia originates from Greek that means abnormal (*dys*) tone (*tonia*), although tone is not always abnormal in dystonia. "Dystonia can be classified by the affected body region(s) as focal if it affects a single

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body part, segmental if it affects one or more contiguous body parts, multifocal if it affects two or more noncontiguous body parts, generalized if it affects one leg and the trunk plus one other body part, or both legs plus one other body part, and hemidystonia if it affects only one half of the body" (p. 624).[10] Dystonia is often classified by etiology as primary when it is the most salient feature of an identified genetic disorder or the origin is unknown, and secondary when it is a symptom of another known underlying disease, such as brain injury, encephalitis, vascular diseases, autoimmune disorders, cerebral malformations, metabolic disease, and neurodegenerative disease.[6,10–12] In children, dystonia is more commonly secondary and thus usually represents a symptom caused by an underlying brain disorder. Certain dystonia syndromes such as occupational hand cramps or blepharospasm are rare in children, but torticollis and opisthotonus occur more frequently.[10,11]

Pathophysiology

Dystonia has been associated with injury to the basal ganglia.[13–15] According to one model, dystonia arises from a net decrease in firing of inhibitory neurons projecting from the internal segment of globus pallidus to the ventral thalamus, causing an increase in the activity of excitatory thalamocortical projections to motor and premotor regions of the frontal cortex.[16] In some cases, however, no basal ganglia injury can be identified and recent evidence from both humans and animal models suggests that other brain areas including cerebellum,[17–20] brainstem,[21] or sensory cortex[22,23] can be causes of dystonia.

The presence of abnormal postures that are superimposed upon or substitute for voluntary movements is a characteristic feature of dystonia. Dystonic postures are repeated and include particular patterns or postures and are characteristic of each child at a given point in time. There are certain common postures that may occur in many different children. Postures can be sustained or brief. Dystonic postures are often triggered by attempts at voluntary movement or voluntary posture. The severity and quality of dystonic postures may vary with body position, specific tasks, emotional state, or level of consciousness.[5,6]

Dystonia can be a cause of hypertonia, although there are other causes of hypertonia.[1] Hypertonia is defined as abnormally increased resistance to externally imposed movement about a joint.[5] Hypertonia associated with dystonia was previously thought to be the result of tonically co-contracting muscles that contribute to passive joint stiffness,[5] but more recent studies suggest that reflexes may play a more important role in hypertonic dystonia[24] (see further discussion below). Hypertonic dystonia differs from hypertonia caused by spasticity, which is a velocity-dependent resistance of a muscle to stretch, often associated with a threshold speed or joint angle for activation.[5]

It is difficult to determine the relative contribution of dystonia and chorea to hyperkinetic movements, and it is possible that hyperkinetic movements primarily occur due to superimposed chorea. Chorea is defined as "an ongoing random-appearing sequence of one or more discrete involuntary movements or movement fragments" (p. 1542).[6] Yet it is also possible that dystonia is a cause of hyperkinetic movements by inserting dystonic postures that result in movements of a part of the body away from the intended movements. If multiple brief dystonic postures are inserted in voluntary movements, this could result in variable, jerky, and tremulous movements. If sustained dystonic postures are inserted in voluntary movements, this could result in the impediment of movement, substitution of an unwanted posture for an intended posture, or slow movement in an attempt to overcome the inserted dystonic posture. It has been shown that hyperkinetic and unwanted movements in upper extremities in children with dyskinetic CP are characterized by increased signal-dependent noise (SDN) of the motor system.[25–27] The SDN theory states that noise in motor commands (e.g. spatial variability) tends to increase with the motor command's magnitude (e.g. force, velocity).[28–30] This means that children with dystonia require significantly slower movements to contain the increased motor variability if they want to achieve comparable precision to typically developing children.[25,27] The relationship between basal ganglia injury and increased signal-dependent noise is not known. Nevertheless, based on the theory that the basal ganglia are responsible for the selective reinforcement of desired muscle patterns and inhibition of undesired muscle patterns,[31,32] basal ganglia disease might lead to decreased inhibition or perhaps even excitation of unwanted patterns, resulting in increased motor variability.[5,26,33]

Although co-contraction is normally identified as a feature of dystonia,[34,35] co-contraction is not necessary for the maintenance of stable postures, either for voluntary postures or for dystonic postures. Co-contraction may not be as frequently present in children with dystonia as originally thought,[36] and in some cases co-contraction could represent voluntary compensation. For example, if the elbow flexion muscles are activated as part of a dystonic posture, the child may activate the extensor muscles voluntarily in an attempt to overcome the involuntary flexion. It would be difficult to distinguish this situation from involuntary dystonic co-activation of the flexors and extensors.[6]

Although co-contraction may contribute to hypertonia in some patients with dystonia, the role of reflex activation has been investigated as another possible contributor.[24] van Doornik and colleagues[24] reported an involuntary or reflex muscle activation in response to stretch, suggesting that this involuntary activation might be a significant contributor to increased tone in hypertonic dystonia. They proposed that this activation might be more important than co-contraction for determining the resistance to passive movement. The important role of reflex stabilization seems more likely in view of the observation that dystonic postures often maintain joints at a mid-range of joint angle, which, in the absence of reflexes, would require improbably precise matching of flexor and extensor torque.

Another disabling feature characteristic of dystonia is overflow: the close temporal association of unwanted muscle contractions with an intended movement. In many circumstances it is the apparent spread of motor activation to surrounding or distant muscles different from those typically appropriate for the goal-directed action. Overflow may also trigger a dystonic posture during voluntary movement. The mechanism of overflow in dystonia is not well understood but theoretical and neurophysiological studies suggest overflow could be due to poor awareness of muscle activation, such that during actions related but unwanted muscles or motor programs are not suppressed adequately.[5,31,37,38]

New insights suggest that dystonia could originate from a lack of reliable sensory feedback regarding motor actions.[39] In particular, dystonia could stem from distorted and excessive afferent inputs linked via reflexes to create abnormal motor outputs.[40,41]

Evaluation

Clinical measures

Discriminating dystonia in children is complex and requires careful observation and knowledge of the disorders commonly concurrent with dystonia, such as spasticity, weakness and bradykinesia.[5] Therefore, sensitive clinical measures become essential to distinguish dystonia from other pediatric movement disorders and to plan for optimal care. A thorough neurological examination in