Pediatric movement disorders

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Purpose of review

Pediatric movement disorders are a heterogeneous group of symptoms that occur in the context of a large number of different neurological diseases. Accurate diagnosis and quantification of these disorders is essential for determining outcome, appropriate treatment, and criteria for inclusion in research trials. The purpose of this review is to summarize recent advances in diagnosis and treatment for childhood movement disorders.

Recent findings

The ultimate goal is to discover new treatments that can lead to measurable improvement in functional outcome for affected children. In order to accomplish this goal, we must have consistent definitions and accurate measurements to determine the diagnosis and severity for each child in a clinic or research trial. Recent progress in defining childhood movement disorders has led to consensus definitions of different types of hypertonia. There has also been progress in the development of outcome measures that relate to meaningful functional performance in a variety of skill areas. Most exciting is the prospect of new treatments, and we survey the current non-medical, medical, and surgical therapies for childhood motor disorders.

Summary

Although pediatric movement disorders are a complex and often poorly understood group of symptoms, recent work has shown that there is a possibility of defining, measuring, and ultimately treating these debilitating diseases.

Keywords

movement disorders, dystonia, spasticity, rigidity, myoclonus, ataxia, tremor, chorea, athetosis, pediatric, childhood, treatment, diagnosis

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Introduction

Adult movement disorders frequently share terminology with the symptoms of those disorders, so that 'parkinsonism' occurs in Parkinson's disease, 'dystonia' occurs in primary torsion dystonia, 'chorea' occurs in Huntington's chorea, and so forth. In children, movement disorders are more commonly symptoms of other diseases. For example, dystonia may be the secondary result of any of a large number of static or progressive diseases, and categorization of the type of symptom is only one of many steps needed to determine an etiologic diagnosis. Tic disorders are an important exception, but we will not discuss tic disorders further in this review.

Childhood movement disorders frequently involve dystonia or spasticity. 'Negative symptoms' (defined below, and including weakness, ataxia, and poorly differentiated control) are also an extremely frequent contributor to disability. The most common cause of movement disorders in children is cerebral palsy, but this disease should be understood as a very heterogeneous group of disorders caused by static injury to one or more motor systems of the brain. A variety of genetic or metabolic diseases in childhood can present with movement disorders such as dystonia or parkinsonism [1–7]. The similarity of symptoms attributable to different neurological diseases suggests that, whatever the mechanism of injury, damage to motor systems of the brain is reflected by a 'final common pathway' of motor disorders for which there is only a limited number of different characteristic deficits. The nature of the symptoms may be more determined by the anatomical location of injury than by the precise mechanism.

The reason for the difference in epidemiology between child and adult disorders is likely to be due to the different effects of injury on the developing compared with the adult brain. For example, hypoxic injury in the prenatal period can have very different effects from later hypoxic injury [8••]. As another example, decreased dopamine in children and young adults appears to be able to cause either dystonia or parkinsonism [9•,10–17], whereas later in life primarily parkinsonism occurs [18] with dystonia in parkinsonian adults existing primarily as a symptom related to treatment with dopaminergic medicines. An unchanging injury in childhood can present with variable or progressive symptoms due to effects of growth and development [19], and the effect of a fixed injury may change over time [14,15,20,21].

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The lack of effective disease-specific treatments and the similarity of symptoms caused by different childhood diseases has led to a search for therapies that may be symptom-specific rather than disease-specific. This effort has been hampered by a lack of consistent definitions of symptoms and a lack of quantifiable measures of the severity of symptoms. It has also been difficult to determine the extent to which any given symptom contributes to a child's disability. In the subsequent sections, we will discuss the relationship between specific impairments and disability, and we will review recent developments in definition, quantification, and treatment of childhood motor disorders.

Functional goals

In the absence of effective and risk-free treatments for many of the diseases that cause movement disorders in children, it becomes essential to categorize and prioritize goals for functional improvement [19]. The National Center for Medical Rehabilitation Research (NCMRR) has recommended the use of a five-axis scale, in which pathophysiology (the disease process), impairment (clinical signs and symptoms), functional limitation (specific limitations of movement), disability (limitations in particular tasks), and societal participation (ability to participate in age-appropriate activities) are included as separate elements describing the impact of disease [22,23]. This classification reminds us that treatment at one level does not necessarily lead to improvement at other levels. For example, reduction of spasticity (an impairment) does not necessarily lead to improvement in an abnormal gait (a functional limitation) although it may contribute to ease of transfers to or from a wheelchair (a disability) and ultimately to greater ability to get to and from school (societal participation).

Selection of appropriate functional interventions for childhood movement disorders is complicated by the observation that children frequently have more than one type of symptom as a result of their underlying disease [24]. Determining the relationship between particular symptoms and the child's functional goals becomes important for determining which symptom to approach first as a target for treatment.

The mixed symptoms in children also complicate the selection of subjects for clinical research trials. By far the largest single group of children is the group with cerebral palsy. However, the variability of symptom type and severity in this group makes it very difficult to obtain a homogeneous sample, and research studies are often forced to confine subjects to a subset (such as hemiplegic cerebral palsy) or a related disorder with 'pure' forms of particular symptoms (such as hereditary spastic paraplegia). No matter what the difficulties, appropriate categorization of children is required in order to determine the effect of intervention and measure functional outcome [19].

Although not usually listed along with other movement disorders, the negative symptoms frequently present in childhood motor disease may be a more significant contributor to disability than the 'positive symptoms'. Negative symptoms are usually taken to indicate the lack of a particular function, rather than the addition of an excess or uncontrolled movement. In many situations, the distinction is difficult. Typical examples of negative symptoms include weakness, ataxia, apraxia, and poor differentiation of individual movements (this last category may be better classified as an apraxia in some cases).

Types of childhood movement disorders

Classically, the movement disorders have been considered to include ataxia, athetosis, chorea, dystonia, myoclonus, bradykinesia, tics, and tremor (dystonia is recognized to have many different manifestations, including dystonic spasms, dystonic tremor, repetitive movements, abnormal fixed postures, and hypertonia, and it may well be that athetosis in children is a particular expression of dystonia). Although this terminology is prevalent in the adult movement disorders literature, for children it is important to include the negative symptoms as well. It is equally important to consider the role of spasticity, both as a diagnostic finding and as a potential cause of disability. It may be helpful to use the term 'motor disorder' to indicate any impairment of movement, whether including positive or negative symptoms, and not limited to the 'movement disorders' that are more familiar to the adult neurology community.

Research in human motor control suggests that voluntary movement can be divided into a planning phase and an execution phase [25–28]. Therefore, when considering childhood movement disorders, it may be helpful to consider whether a particular disorder is more likely to relate to planning (e.g. apraxia) or execution (e.g. weakness). We must also consider disorders for which there is excessive movement that is not triggered by volition (e.g. myoclonus). Finally, we must consider those disorders that are readily apparent to a clinician but which do not necessarily interfere with voluntary movement (e.g. spasticity).

Thus in some cases it may be helpful to separate childhood movement disorders into four primary categories: (1) disorders of tone, (2) disorders of inhibition of movement, (3) disorders of execution of movement or posture, and (4) disorders of movement planning. Disorders of tone are signs observed by the clinician during a neurological examination. These disorders do

not describe the results of voluntary movement, and they may be more important as diagnostic tools than as determinants of disability. Disorders of inhibition are disorders in which movement is initiated without the child's intent. The result is extra movement that occurs either at rest or associated with movement, but which is not closely linked to the particular movement being performed. Disorders of execution are disorders in which the pattern or magnitude of muscle activation is not appropriate for the intended task. This will lead to a movement which does not correspond to the child's plan. Disorders of planning are disorders in which the muscle activations are appropriate for the intended movement plan, but the movement does not accomplish the desired task. Under this taxonomy, it may not always be possible to assign a particular disorder to a single category. For example, ataxia is likely to be a disorder both of execution and planning. Dystonia may cause an abnormality of tone, but it also affects movement execution, and hypertonic dystonia could be due to a lack of inhibition of antagonist muscle activity. In young children or in children with cognitive deficits it may be difficult to distinguish between disorders of planning and execution. To illustrate the categories, in Table 1 we have attempted to place examples of specific disorders within the category that best describes the effects of the disorder.

The last category in Table 1, disorders of planning, is perhaps the least well-understood of the childhood motor disorders. It is not known whether the adult classification of apraxia (ideational, ideomotor, and limb-kinetic [29,30]) applies to children. It is not known whether speech apraxia [31–33] is related to apraxia involving arm or hand movements. Furthermore, it is not known whether developmental coordination disorder [34] is a separate entity from apraxia. Finally, it is not known whether poorly differentiated control is due to apraxia, ataxia, dystonia, or possibly a combination of multiple symptoms including weakness. Disorders of sensation can lead to many different abnormalities of planning or execution [34], and whether these should be considered separately should be investigated [35–37].

Table 1. Categorization of specific childhood movement disorders

Category	Disorder
Disorders of tone	Spasticity and clonus
	Dystonia
	Rigidity
	Hypotonia
Disorders of inhibition	Chorea
	Myoclonus
	Tics
	Tremor
Disorders of execution	Weakness
	Bradykinesia
	Dystonia
	Ataxia
Disorders of planning	Apraxia
	Developmental coordination disorder
	Poorly differentiated control
	Disorders of sensation

Advances in defining childhood movement disorders

One of the most salient diagnostic features of many childhood motor disorders is the presence of increased tone. There has been disagreement between practitioners of different fields concerning the appropriate labeling of different types of childhood hypertonia. A US National Institutes of Health-sponsored taskforce recently proposed a set of consensus definitions for spasticity, dystonia, and rigidity as they apply to childhood hypertonia [19]:

'Spasticity is defined 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.'

'Dystonia is defined as a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both.'

'Rigidity is defined 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.'

It is expected that the consensus definitions will evolve with time as further information becomes available from basic science and clinical research trials. The existence of the consensus document demonstrates the ability to reach common definitions between clinicians and researchers from different fields. We expect that similar projects will need to be undertaken in order to define hyperkinetic disorders, negative symptoms, and other components of childhood motor impairment. There has recently been an attempt to re-evaluate the classification of cerebral palsy, and this has led to a consensus statement of algorithms for classification of subtypes of this particular disorder [38].

Advances in quantifying childhood movement disorders

Quantification of movement disorders is important in order to be able to determine the effectiveness of therapy in individual children, as well as to determine the outcomes of clinical research trials. Quantification can be performed at different levels of the NCMRR scale, and measures tend to reflect either the degree of impairment, functional limitation, or disability.

Tests of impairment usually are directed at measuring hypertonic symptoms [39,40]. Dyskinetic, ataxic, or other symptoms have been less well studied. Certainly strength is measurable, and kinematics and dynamics have been best evaluated in the context of gait analysis [41,42]. Rating scales for dystonia have been developed in adults and children [43•,44].

There has been significant recent progress in the development of functional measures of motor performance in children. Recent scales include the Melbourne [45,46] and QUEST (Quality of Upper Extremity Skills Test) [47] scales for testing the upper extremity. The GMFM (Gross Motor Function Measure) and GMFCS (Gross Motor Function Classification System) are validated scales that can predict long-term function [48••].

There has also been significant progress in the development of disability outcome ratings. These ratings attempt to measure a child's performance of activities of daily living, or participation in age-appropriate activities. Outcome scales were reviewed by Lollar *et al.* [23].

Advances in therapy

Medical therapy for movement disorders has traditionally been more successful at reducing positive symptoms than it has been at improving negative symptoms. This does not represent an essential limitation in the ability to improve impairment, but rather represents the effects and limitations of medical and surgical intervention. Nevertheless, there have been significant improvements in our understanding of treatment of positive symptoms [49].

Spasticity has long been considered to be a primary determinant of disability. Recently, questions have been raised as to whether the degree of spasticity is in fact closely related to the degree of disability [50]. Certainly, extreme spasticity can lead to an immovable joint and therefore reduction could be expected to improve function. It is more difficult to predict the effects of intervention in milder cases. Medical therapy of spasticity has been directed at multiple components of monosynaptic or polysynaptic spinal reflex pathways. Medications such as baclofen, clonidine, or tizanidine are presumed to reduce spinal motoneuron excitability and thereby reduce the effect of spasticity. Recent studies of baclofen given by intrathecal infusion pump have shown substantial success in some cases [51,52]. Dantrolene reduces the effect of muscle contraction. Selective dorsal rhizotomy reduces the effect of spindle afferents on motoneuron pools and a recent review [53•] suggested benefits for appropriately selected children. Botulinum toxin reduces the effect of motor neurons on muscle fibers, and may also reduce the contraction of spindle fibers and afferent feedback from stretch receptors. The advent of botulinum toxin therapy for children has led to substantial benefits for many children, and this has been verified in several functional outcome studies, reviewed by Graham *et al.* [54].

Dystonia has proven to be resistant to treatment in many cases. Trihexyphenidyl has long been the mainstay of treatment in adults and children [55], and blinded clinical trials in adults showed that it is probably efficacious at doses much higher than originally recommended for the treatment of idiopathic Parkinson's disease [56,57]. The use of trihexyphenidyl in children is more recent, with a retrospective study [58] documenting its probable effectiveness. The mechanism of action is unknown, and it does appear that, as for adults, the doses in children need to be substantially higher than originally recommended. Tetrabenazine has been helpful in the treatment of tardive dystonia, but its effectiveness in childhood primary or secondary dystonia has been disappointing [59–64]. The discovery of dopa-responsive dystonia (Segawa's disease [17]) has led to many children receiving trials of dopaminergic medication prior to the initiation of other therapy. One consequence of this has been the observation that many children with cerebral palsy or other motor disorders have responded to dopaminergic medication despite the lack of a consistent theory to explain why this might be so. An open-label trial has shown very encouraging results [65] and a controlled clinical trial is now under way. One of the most exciting advances in adult idiopathic torsion dystonia has been the discovery that deep-brain stimulation of the internal globus pallidus can lead to substantial improvement. This discovery follows a long tradition of stereotactic neurosurgery for dystonia [66,67], and lesions in the thalamus may also be effective [68]. There is increasing evidence that deep-brain stimulation of the internal pallidum may also be helpful in children with both primary (genetic) and secondary dystonias, although the results in secondary dystonias have been less successful [69–71]. This intervention requires significant further study, and the long-term effectiveness of deep-brain stimulation or stereotactic lesions has not yet been adequately investigated. Although originally developed for the treatment of spasticity, there is recent evidence that intrathecal

baclofen may also have benefit in some children with dystonia [72–74].

Treatment of both chorea and myoclonus in children has been frustratingly difficult, and there are no published controlled trials. Both of these disorders occur frequently in the context of encephalitis or post-encephalitis, and treatment is usually directed at the underlying disease. Piracetam has long been available in Europe for the treatment of myoclonus, and the introduction of the related medication levetiracetam in the United States suggests that this may provide a new therapy. The role of serotonin precursors or agonists in childhood myoclonus is not known, although there have been reports of success in the treatment of adults. Chorea in children is most commonly treated with medications that potentiate or stimulate γ-aminobutyric acid (GABA) receptors, including clonazepam and valproate. In adults, chorea may be susceptible to treatment with dopamine receptor antagonists or tetrabenazine, although there have not been studies in children [59,60]. Thalamic deep-brain stimulation is a promising modality that will require further studies [75].

Perhaps the most exciting advances in the treatment of childhood motor disorders have come from non-medical interventions. There has long been concern that strengthening a hypertonic muscle could potentially lead to a worsening of symptoms. However, in children with spasticity this does not seem to be the case and in fact there is no clear relationship between spasticity and strength [50,76••]. Strengthening exercise can thus lead to functional improvement [77,78,79••]. It has remained difficult, however, to show that physical therapy is effective for all children [80]. Some negative symptoms including lack of coordination or balance can be improved with training that involves the necessity of maintaining posture on an unsteady base. A particular example is the use of hippotherapy (horseback riding) for children with impairments of trunk strength and tone [81,82]. The use of thin neoprene or Lycra vests may improve trunk stability and reaching in some children [83,84]. Maintenance of activity and participation in age-appropriate activities is thus likely to be an extremely important component of functional improvement. It is possible that part of the effectiveness of this approach is in fact due to functional reorganization of motor areas in the brain. The most convincing example of this comes from the use of constraint therapy, in which an artificial restriction of the 'good' arm of a stroke patient may lead to improved function of the plegic arm along with enlargement of the cortical representation [85,86]. Further research is needed to determine if this mechanism is applicable to children, but early results are promising [87,88].

Conclusion

Childhood movement disorders remain a frustrating set of symptoms. Nevertheless, there has been significant recent progress in classification, measurement, and treatment of these disorders. There is a tremendous need to continue these efforts in order to provide an accurate and consistent classification for the different components that lead to disability. This effort is not the province of any one clinical specialty, but needs to be a joint effort between all the specialties that are concerned with the treatment of motor-impaired children. There is a tremendous need for blinded clinical trials to evaluate the effect of the interventions that are available today. Ultimately, we must work to develop and test new therapies that can eventually lead to meaningful improvement in functional outcome for affected children.

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