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Special Concerns in Defining, Studying, and Treating Dystonia in Children

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Abstract

Dystonia is movement disorder with many diverse underlying etiologies. Some of those etiologies manifest at specific stages of development or at specific ages. Others may present early in life and evolve as the individual develops. Appearance of symptoms during a time of nervous system development poses special challenges to the neurology. Normal functions change appearance, dysfunction may manifest in an age-dependent manner, and age-dependent differences in beneficial and toxic effects of treatments all introduce complexities to the process of diagnosis, functional assessment, and therapeutics. Consideration of these developmental differences is essential in assuring a universal definition of dystonia, valid and reliable assessment tools that can be compared across the lifespan, and more effective therapeutics.

Keywords

Rating Scales; Development; Treatment; Pediatrics

It has become a mantra in the fields of pediatric medicine and child development that "children are not just little adults." That statement reminds us of the complex biological changes that occur during development from fetus to fully mature adults. In no field is it more applicable than in neurology. The changing appearance of normal functions, the age-dependent manifestations of dysfunction, the onset of specific disorders in certain age groups, and age-dependent differences in beneficial and toxic effects of treatments pose challenges to the neurologist. Movement disorders comprise an especially challenging set of disorders to define, assess, and treat in children of various ages. In this issue of *Movement Disorders*, other articles discuss the challenges in defining, assessing, and treating dystonia. This article will focus on the particular challenges presented by dystonia at different stages of development.

Can we use the same definition of dystonia in adults and children?

In general the answer is probably yes, but two special possible exceptions deserve consideration. The first is when dystonia is so severe and sustained that it manifests more as hypertonia than as abnormal movements. The second is in developmentally normal younger children who have overflow as part of their immature motor patterns, or transient conditions that have dystonia-like manifestations but are best not classified as "dystonias".

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The Definitions of Dystonia and Dystonic Hypertonia

The definition of dystonia has evolved substantially since the first use of the term by Oppenheim in 1911[1]. The various attempts comprehensively to define "dystonia" are review in this issue of *Movement Disorders*[2]. Although Oppenheim's classic report described a form of dystonia starting childhood, efforts to develop a comprehensive yet specific definition have mostly focused on dystonia in adults. However, the early-onset dystonia described by Oppenheim (now generally referred to as DYT1 dystonia) continues to represent the iconic form of dystonia. The most recent definition of dystonia has attempted include both mono-symptomatic dystonic disorders (isolated dystonia) and those characterized by a combination of dystonia and other movement disorders (combined dystonia)[2], but isolated dystonia remains the basis for the specific definition. Of note, the word *tone* does not appear in the definition despite the root of the term *dystonia* because dystonia is not a disorder of tone in isolated forms. That definition is as follows:

> "Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation."

This definition is a refinement of the definition provided by the *ad hoc* committee of the Dystonia Medical Research Foundation (DMRF) in 1984[3].

During the period of years over which the DMRF definition was applied, the field of movement disorders neurology saw a tremendous explosion in knowledge and prominence as a sub-specialty of neurology. This was not true in the field of child neurology. Some child neurologists, including John Menkes, MD and Emilio Fernandez-Alvarez, MD, had an abiding interest in dystonia and other movement disorders, but the large-scale efforts within the movement disorders community to increasingly specify the definitions of the various movement disorders went largely unrecognized in child neurology. Conversely, child neurologists played little role in developing and refining the definitions. The result was to the detriment of both fields.

By 2001, a small group of specialists, from a variety of fields, who studied and cared for children with mixed motor disorders falling under the category of cerebral palsy (CP) began to recognize a disparity in the application of terminology when classification different aspects of the motor impairment. Upon viewing videos of children with CP, the group rarely agreed upon whether the abnormal movement patterns were due to dystonia, spasticity, a combination, or something else. Recognizing an urgent need to develop better definitions that applied well to children with mixed disorders and to reach consensus across the specialties caring for these children (neurology, neurosurgery, orthopedics, development pediatrics, physical therapy, and occupational therapy), the Taskforce on Childhood Motor Disorders was convened. An initial interdisciplinary workshop was held at the National Institutes of Health in April, 2001. Over almost 10 years, the Taskforce worked to develop consensus on broad categories of movement disorders in children, including types of hypertonia[4], types of negative motor signs[5], and types of positive motor signs[6] that exist in children with mixed motor disorders. The goals were not only to provide specific definitions, but to formally test the ability to apply those definitions in the clinical evaluation of children with mixed motor disorders.

It quickly became apparent that children with severe dystonia, either alone or in combination with other movement disorders, often had hypertonia of a dystonic type. As noted above, tone does not play any role in the DMRF definition of dystonia or in the current modification. Isolated dystonia is rarely, if ever, accompanied by abnormal tone in the

affected body part(s) and when it does the tone is typically mildly low. However, in some children with CP and in children with a variety of metabolic disorders (e.g. pantothenate kinase-associated neurodegeneration, glutaric aciduria, Leigh syndrome), the dystonia is so severe that the major manifestation is one of hypertonia rather than a movement disorder. In recognition of this, the Taskforce defined dystonia twice.

The definition of dystonia was based on the 1994 DMRF definition of dystonia:

> *"Dystonia in childhood is a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both. Dystonia is commonly triggered or exacerbated by attempted voluntary movement and may fluctuate in presence and severity over time. The severity and quality of dystonic postures may vary with body position, specific tasks, emotional state, or level of consciousness."*[4, 6]

The Taskforce then specified the definition of *dystonic hypertonia*:

> *"Hypertonia caused by dystonia is the result of tonically contracting muscles that contribute to passive joint stiffness as a result of the force generated by the initially active muscle fibers. Dystonia is a cause of hypertonia only when there is muscle activity when the child is at rest and the limb is supported against gravity, or when muscle activity begins before the onset of externally imposed passive joint movement."*[4]

While there is no direct conflict between the Taskforce and DRMF definitions, the Taskforce definition recognizes that dystonia may manifest as hypertonia in severely affected children with dystonic disorders and creates a separate category for dystonic hypertonia. The Taskforce definition of dystonic hypertonia was used to create an assessment tool that was shown to have good validity[7]. It was further tested using quantitative kinematic methods and also found to have good cross validity as compared with the Taskforce definition of spasticity[8]. Despite these encouraging data, the validity of dystonic hypertonia in adults remains to be demonstrated. Furthermore, the therapeutic implications of dystonic hypertonia require investigation, but it would follow that treatments for dystonic hypertonia are likely to differ from those for spastic hypertonia. Nevertheless, expansion of the definition of dystonia to include dystonic hypertonia could provide a more comprehensive definition that might be applied more universally across conditions and ages.

Normal Developmental Processes, Transient Manifestations, and Pseudodystonias

The normally developing nervous system produces a variety of motor patterns that would be considered pathological in older children and adults. These seem similar to the well-known 'primitive' or neonatal reflexes that are present in neonates and disappear in a developmentally determined order as the nervous system matures[9], but may reemerge in adults following cerebral injury or degeneration. Thus, a normal toddler will have overflow movements that appear dystonia. These diminish as development proceeds, but may be brought out in a school-aged child challenging tasks such as walking with the feet inverted or everted[10].

Transient or developmental conditions characterized by dystonia posture or movements may reflect transiently abnormal neuronal function, but do not correlate with serious underlying pathology. Most of these conditions occur during infancy or early childhood and typically resolve with no dystonic sequelae. Examples include paroxysmal tonic upgaze of infancy[11], benign paroxysmal torticollis[12], and benign idiopathic dystonia of infancy[13].

Other conditions are better classified as pseudodystonias[2]. Pseudodystonia may look like dystonia but are due to identifiable structural, physiologic, or behavioral factors. Examples

of pseudodystonias manifesting in childhood include Sandifer syndrome[14], congenital torticollis[15], fourth cranial nerve palsy[16], and infantile masturbation[17].

Perhaps these conditions are excluded by the definitions of dystonia including the words *disorder* and *abnormal*, but whether to label a condition as a "disorder" or "abnormal" is not always obvious during routine clinical evaluations. Most child neurologists recognize these disorders readily, but extensive investigations are pursued in some cases. Adult movement disorders neurologists may be less likely to recognize the benign conditions as benign.

Can we apply the same dystonia rating scales to children and adults?

There does not appear to be a perfect dystonia rating scale with rigorously demonstrated validity, reliability, and utility across multiple forms of dystonia including generalized, focal, isolated, and combined. The challenges of rating scale development, testing, and implementation for dystonia have been reviewed elsewher[18]. A few rating scales for dystonia, or that include dystonia, have been developed for use primarily in children. These include Barry-Albright Dystonia Scale (BADS)[19], and the Movement Disorder – Childhood Rating Scales (MD-CRS)[20, 21]. The BADS was developed for assessing outcomes following intrathecal baclofen treatment of secondary dystonia. The MD-CRS was designed as two versions, one for children age 0 – 3 years[20] and the other for children age 4 – 18 years[21] regardless of the specific movement disorder. The MD-CRS has been shown to have good construct validity and inter-rater reliability, but does not separate out specific movement disorders nor does it discriminate among them.

The most widely used dystonia rating scale is the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). The BFMDRS was designed for use in primary generalized dystonia and was initially tested in older children, adolescents, and young adults[22, 23]. However, no scale has been tested rigorously to determine the validity across a broad range of development, including young children. Many dystonic disorders begin in infancy or early childhood. Thus, comprehensive natural history studies of progression, response to treatment, or functional impact of specific disorders will require assessment across the lifespan starting with age at onset of symptom. Using different instruments at different ages may be justifiable if sufficient cross-validation and calibration is performed.

Childhood-specific obstacles must be overcome for any rating scale to be broadly applicable in both children and adults. These include 1) accounting for normal developmental manifestation of dystonic-like movement patterns (see previous section), 2) including developmentally appropriate tasks at different ages, and 3) accounting for the normal development of motor control. In addition, since most children with dystonia have other movement disorders, a valid and reliable method to dissociate dystonia from other movement disorders in children (and adults) with mixed motor disorders (combined dystonia) is essential.

Experimental Therapeutics and Treatment Considerations

It is generally known that modifications of medication dosing must be made for children. Dosing is typically weight dependent, but even weight-based dosing must be modified for children of different ages. Absorption, distribution, and metabolism may all change with age depending on developmental factors. In recognition of the complexities of pharmacotherapy in children and the perils of extrapolating from adult dosing guidelines, the United States has two relatively recent laws that direct research and regulatory policy for children. These are the "Best Pharmaceuticals for Children Act", and the "Pediatric Research Equity Act". Unfortunately, many of the most frequently used medications for treatment of movement disorders have not been tested in children of different ages in a systematic manner or with an

eye toward safety. Nevertheless, they are used in children “off-label” for pediatric movement disorders, including dystonia.

The most commonly used oral medications for treating dystonia in children are trihexyphenidyl, baclofen, and carbidopa/levodopa[24]. Of these, only baclofen has United States Food and Drug Administration (FDA) approved dosing for children. Botulinum toxin is also used to treat dystonia in children, but it also is not FDA approved for use in children. Dosing recommendations for children have been published for each of these medications, but they are based on either small studies or expert opinion. High quality evidence on which to base dosing in children is lacking.

Evaluating adverse effects is potentially even more complicated than evaluating efficacy in children. The most bothersome side effects from medications used to treat dystonia are often cognitive. Pre-verbal or non-verbal children are unable to complain of cognitive side effects. Thus, more object assessments may be required. It is also likely that younger children lack the experience and reasoning ability to identify cognitive impairment in themselves or to attribute difficulty to specific medications. It is a common view among movement disorders neurologists that children can tolerate substantially higher doses of trihexyphenidyl without bothersome cognitive side effects than can adults. Indeed, in the classic study of Burke et al., the average age of subjects who complained of cognitive side effects was 24 years and the average age of those who did not have cognitive side effects was 17 years[22]. However, our personal experience has shown that children age 8 – 15 years with DYT1 dystonia had substantial decline in school function during treatment with trihexyphenidyl even though they did not report cognitive side effects[25]. This underscores a need for more objective and systematic assessment of adverse effects of treatment in children.

The influence of age and brain development on neuromodulatory therapy such as deep brain stimulation (DBS) must also be considered. Globus pallidus DBS is used increasingly to treat dystonia in young children[26–28] with results ranging from dramatic to modest. Although some children have been shown to have enduring benefits, the effect of continuous high frequency stimulation on brain development is not known. One potential mechanism of DBS action is alteration of abnormal neural plasticity. If DBS alters abnormal plasticity, it is possible and even likely that it alters normal plasticity as well. While no harmful effects on development have been reported, there has been scant attention to this potential concern.

Unmet Clinical Needs of Children with Dystonia

The major unmet need of children with dystonia, especially those with dystonia secondary to structural brain lesions or to metabolic disorders, is the availability of effective symptomatic treatment. Pharmacologic treatments and DBS are less effective in children with secondary dystonia than in children with primary dystonia[27, 29]. This may relate to many factors including the underlying pathobiology, age at symptom onset, and coexistence of other neurologic signs and symptoms. Nevertheless, there are many children in whom dystonia is the major cause of disability who have inadequate benefit from currently available treatments. Most dystonia treatments are designed for and tested first in primary dystonia. This is not a problem for patients with primary dystonia, but the ability to extrapolate findings to guide development of treatments for secondary dystonia is limited. Thus, there is a substantial need for further experimental therapeutics research on dystonia in children.

The lack of universally valid rating scales has contributed to the paucity of experimental therapeutics research in childhood dystonia. Furthermore, the lack of valid methodology to assess dystonia when it is combined with other movement disorders has limited the focus of research to specific disease entities or to primary dystonia in children. Thus, the

development of valid and reliable instruments for use in children of many ages is a critical need.

Finally, there is a need to better understand the pathophysiology of dystonia across different forms. Because the characteristic clinical manifestations of dystonia are present in a wide variety of disorders, it seems logical to hypothesize a common mechanism. However, because dystonia seems to result from disordered function of complex neural circuits it is likely that dysfunction arising at any one (or several) node in those circuits may results in similar manifestations. Yet, effective treatment may differ across disorders depending on which node is primarily affected. This may be especially true for DBS. In children, the different etiologies or the evolving development of circuits may require different targets or stimulation parameters for one type of dystonia than for others.

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References

1. Oppenheim H. Über eine eigneartige Krampfkrankheit des kindlichen un jugendlichen Alters (Dysbasia lordotica progressiva, Dystona musculorum deformans). Neurologishe Centralblatt. 1911; 30:1080–1107.
2. Albanese A, Bhatia K, Bressman SB, et al. Phenomenology and classification of dystonia: a consensus update. Mov Disord. 2013 in press.
3. Fahn, S.; Marsden, CD.; Calne, DB. Classification and investigtaion of dystonia. In: Marsden, CD.; Fahn, S., editors. Movement Disorders 2. London: Butterworth; 1987. p. 332-358.
4. Sanger TD, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Classification and definition of disorders causing hypertonia in childhood. Pediatrics. 2003; 111(1):e89–e97.
5. Sanger TD, Chen D, Delgado MR, Gaebler-Spira D, Hallett M, Mink JW. Definition and classification of negative motor signs in childhood. Pediatrics. 2006; 118(5):2159–2167.
6. Sanger TD, Chen D, Fehlings DL, et al. Definition and Classification of Hyperkinetic Movements in Childhood. Mov Disord. 2010; 25(11):1538–1549.
7. Jethwa A, Mink J, Macarthur C, Knights S, Fehlings TDF. Development of the Hypertonia Assessment Tool (HAT): a discriminative tool for hypertonia in children. Devel Med Child Neurol. 2010; 52(5):e83–e87. [PubMed: 20540176]
8. Gordon LM, Keller JL, Stashinko EE, Hoon AH, Bastian AJ. Can spasticity and dystonia be independently measured in cerebral palsy? Pediatr Neurol. 2006; 35(6):375–381. [PubMed: 17138005]
9. Volpe, J. Neurology of the Newborn. 3rd ed.. Philadelphia: WB Saunders; 1995.
10. Camp JA, Bialer I, Press M, Winsberg BG. The physical and neurological examination for soft signs (PANESS): pediatric norms and comparisons between normal and deviant boys [proceedings]. Psychopharmacol Bull. 1977; 13(2):39–41. [PubMed: 859991]

11. Ouvrier R, Billson F. Paroxysmal tonic upgaze of childhood--a review. Brain Dev. 2005; 27(3): 185–188. [PubMed: 15737699]
12. Al-Twaijri W, Shevell M. Pediatric migraine equivalents: occurrence and clinical features in practice. Pediatr Neurol. 2002; 26:365–368. [PubMed: 12057796]
13. Deonna T, Ziegler A, Nielsen J. Transient idiopathic dystonia in infancy. Neuropediatrics. 1991; 22:220–224. [PubMed: 1775219]
14. Kotagal P, Costa M, Wyllie E, Wolgamuth B. Paroxysmal nonepileptic events in children and adolescents. Pediatrics. 2002; 110(4):e46. [PubMed: 12359819]
15. Collins A, Jankovic J. Botulinum toxin injection for congenital muscular torticollis presenting in children and adults. Neurology. 2006; 67:1083–1085. [PubMed: 17000985]
16. Ballock RT, Song KM. The prevalence of nonmuscular causes of torticollis in children. J Pediatr Orthop. 1996; 16(4):500–504. [PubMed: 8784706]
17. Yang ML, Fullwood E, Goldstein J, Mink JW. Masturbation in infancy and early childhood presenting as a movement disorder: 12 cases and a review of the literature. Pediatrics. 2005; 116(6):1427–1432. [PubMed: 16322167]
18. Comella CL, Leurgans S, Wuu J, Stebbins GT, Chmura T. Rating scales for dystonia: a multicenter assessment. Mov Disord. 2003; 18(3):303–312. [PubMed: 12621634]
19. Barry MJ, VanSwearingen JM, Albright AL. Reliability and responsiveness of the Barry-Albright Dystonia Scale. Dev Med Child Neurol. 1999; 41(6):404–411. [PubMed: 10400175]
20. Battini R, Guzzetta A, Sgandurra G, et al. Scale for evaluation of movement disorders in the first three years of life. Pediatr Neurol. 2009; 40(4):258–264. [PubMed: 19302937]
21. Battini R, Sgandurra G, Petacchi E, et al. Movement disorder-childhood rating scale: reliability and validity. Pediatr Neurol. 2008; 39(4):259–265. [PubMed: 18805364]
22. Burke RE, Fahn S, Marsden CD. Torsion dystonia: a double-blind, prospective trial of high-dosage trihexyphenidyl. Neurology. 1986; 36(2):160–164. [PubMed: 3511401]
23. Burke RE, Fahn S, Marsden CD, Bressman SB, Moskowitz C, Friedman J. Validity and reliability of a rating scale for the primary torsion dystonias. Neurology. 1985; 35(1):73–77. [PubMed: 3966004]
24. Mink, JW. Dystonia (DRD, primary, secondary). In: Singer, HS.; Kossoff, EH.; Hartman, AL.; Crawford, TO., editors. Treatment of Pediatric Neurologic Disorders. Boca Raton: Taylor & Francis; 2005. p. 139-144.
25. Cialone J, Mink J. Globus pallidus deep brain stimulation provides benefit and allows medication reduction in young children. Devel Med Child Neurol. 2012; 54(Suppl. 4):39–40.
26. Haridas A, Tagliati M, Osborn I, et al. Pallidal deep brain stimulation for primary dystonia in children. Neurosurg. 2011; 68(3):738–743. discussion 743.
27. Gimeno H, Lumsden D, Gordon A, et al. Improvement in upper limb function in children with dystonia following deep brain stimulation. Eur J Paediatr Neurol. 2013
28. Gimeno H, Tustin K, Selway R, Lin JP. Beyond the Burke-Fahn-Marsden Dystonia Rating Scale: deep brain stimulation in childhood secondary dystonia. Eur J Paediatr Neurol. 2012; 16(5):501–508. [PubMed: 22258088]
29. Sanger TD, Bastian A, Brunstrom J, et al. Prospective open-label clinical trial of trihexyphenidyl in children with secondary dystonia due to cerebral palsy. J Child Neurol. 2007; 22(5):530–537. [PubMed: 17690057]