Treatment of Disorders of Tone and Other Considerations in Pediatric Movement Disorders

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Abstract

Pediatric movement disorders (PMDs) consist of a heterogeneous group of signs and symptoms caused by numerous neurological diseases. Different neurological disorders in children also share overlapping movement disorders making a diagnosis of the underlying cause of the movement disorder challenging. The similarity of the symptoms across multiple disease types suggests that there may be a final common motor pathway causing the overlapping movement disorders. There are numerous disorders in children associated with disturbances in tone and involuntary movements. This chapter will focus primarily on those disorders that involve abnormalities of tone and other important considerations of pediatric movement disorders. This chapter will address rating scales and goals for treatment and will include a review of symptomatic treatment and, where possible, the treatment of the underlying disease processes. The chapter will review representative disorders, including an inborn error of metabolism, an autoimmune disorder, and a group of neurodegenerative disorders. These examples demonstrate how the disorder's underlying pathophysiology results in a specific approach to the underlying disease and the associated conditions of tone and involuntary movements. Finally, the multiple treatment options for cerebral palsy and considerations of cerebral palsy mimics will be discussed.

Keywords Pediatric movement disorders · Sydenham chorea · Glucose transporter deficiency · NBIA · Cerebral palsy · Treatment · Pediatrics · Childhood

Introduction

Pediatric movement disorders (PMDs) consist of a heterogeneous group of signs and symptoms caused by numerous different neurological disorders. Different neurological diseases in children also share overlapping movement disorders making a diagnosis of the underlying cause of the movement disorder challenging. The similarity of the symptoms across multiple disease types suggests that there may be a final common motor pathway causing the overlapping movement disorders. There are numerous disorders in children associated with disturbances in tone and involuntary movements. This chapter will focus primarily on those disorders that involve abnormalities of tone and other important considerations of pediatric

movement disorders. This chapter will address rating scales and goals for treatment and will include a review of symptomatic treatment and, where possible, the treatment of the underlying disease processes. Several common pediatric disorders will not be covered in this chapter, including tics and Tourette syndrome [1] and isolated dystonia [2], which are covered in other chapters of this special edition.

The classification of movement disorders, in general, can be broken down into hyperkinetic movements, hypokinetic movements, disorders of tone, and negative symptoms. Although hypokinetic conditions, such as Parkinson disease, predominate in adults, children often present with hyperkinetic movement disorders such as tics, chorea, tremor, and myoclonus. Children often have mixed tone and movement disorders more often than adults who tend to have more isolated tremor, dystonia, or parkinsonism. Children also have ongoing brain maturation and development, resulting in differing expressions of the same disease over time. An example of this is the phenotypic heterogeneity of proline-rich transmembrane protein 2 (PRRT2) mutations, which can present as benign familial infantile epilepsy, infantile epilepsy with choreoathetosis, or paroxysmal kinesigenic dystonia [3].

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Disorders of tone often predominate in pediatric disorders of the central nervous system. Spasticity and dystonia, usually in a mixed pattern, are the most common tone disorders seen in children with cerebral palsy (CP). Because involuntary movements may be superimposed on underlying disorders of tone, careful consideration is required when choosing target symptoms for treatment. For example, reducing hypertonia with medications such as baclofen or benzodiazepines may result in a dramatically increased expression of dyskinetic movements in children with athetoid/dyskinetic CP.

Negative symptoms can coexist with hyperkinetic and hypokinetic movement disorders as well as with disorders of tone and posture. Negative symptoms consist of a lack of function rather than the presence of excessive or uncontrolled movements. Examples include weakness, ataxia, and apraxia. Negative symptoms are essential to recognize, as they often significantly contribute to the functional disabilities of children with movement disorders.

PMDs have a variety of genetic and structural etiologies. These etiologies can be further subdivided into those associated with static processes, such as cerebral palsy and those disorders with progressive injury and loss of neurons and glial cells within the central nervous system. The latter are defined as pediatric neurodegenerative disorders. Pediatric neurodegenerative disorders can be further subclassified into those disorders predominantly affecting gray matter structures (e.g., poliodystrophies) and those affecting white matter (e.g., leukodystrophies). Poliodystrophies often present with seizures, retinal degeneration, and dementia, whereas the leukodystrophies most often present with spasticity, ataxia, and cortical visual impairment. As these disorders progress, overlapping features of both forms of neurodegeneration become apparent. In both static and neurodegenerative disorders, various movement disorders can coexist and change over time.

There is a lack of disease-specific treatments in many of the static and neurodegenerative processes. The PMDs associated with neurodegenerative diseases commonly need to be treated based on the specific movement disorder. Priority is always given to those movements causing the most significant degree of functional disability. The goal of functional improvement is the mainstay of treatment. The National Center for Medical Rehabilitation Research recommended a 5-axis scale for the operational management of PMD. These include the pathophysiology of the disease, 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) [4].

Rating scales are essential for conducting clinical research and can be used to extrapolate outcomes in the clinical setting. Many rating scales are specific to the primary form of underlying tone abnormality or the movement disorder experienced. The Gross Motor Function Measure [5] was created in 1989

and has been updated to include either 66 or 86 items as well as age-related percentiles. This scale is generally administered by physical therapists and is intended to document a functional change in children with cerebral palsy over time. The Gross Motor Function Classification System (GMFCS) is an easily administered 5-level clinical classification system that describes the gross motor function of people with cerebral palsy based on self-initiated movement abilities [6]. The Ashworth and Modified Ashworth scales evaluate the degree of hypertonia. These tests are easy to administer, though intra-rater and inter-rater reliability have been criticized as not being reliable [7]. This lack of reliability may be due in part to the fact that the degree of hypertonia often fluctuates depending on the child's state during the evaluation. A more global assessment of PMDs can be quantified using the Movement Disorder-Childhood Rating Scale, which can be used in children and adolescents between the ages of 4 and 18 years. This scale was created to address the limitations of movement specific rating scales as well as the movement disorder rating scales designed for adults. This scale rates motor functioning, dysphagia function, self-care limitations, and attention/alertness issues in children with one or more PMD [8].

Specific Disorders in Childhood Associated with PMDs and Abnormalities of Tone

The following representative disorders, an inborn error of metabolism, an autoimmune disorder, and a group of neurodegenerative disorders, will be used to demonstrate how the underlying pathophysiology of each results in a specific approach to the underlying disease as well as to the associated disorders of tone and involuntary movements. Finally, the multiple treatment options for cerebral palsy, as well as cerebral palsy mimics, will be discussed at length.

Glut-1 Deficiency Syndrome—an Inborn Error of Metabolism

Glut-1 deficiency syndrome is most commonly an autosomal dominant disorder due to deletions or pathological variants of the SLC2A1 gene, which encodes the glucose 1 transporter protein. The protein is intramembranous and allows for the passive transfer of glucose across membranes. It includes the passive transfer of serum glucose through the blood-brain barrier into the cerebral spinal fluid. Patients affected with Glut-1 deficiency syndrome have classically presented with infantile epilepsy associated with medically refractory seizures, developmental delay, acquired microcephaly, hypotonia, spasticity, and a complex movement disorder consisting of ataxia and dystonia. However, other clinical manifestations have been described more recently, such as paroxysmal exertion-induced dystonia with or without seizures, choreoathetosis,

alternating hemiplegia, and other paroxysmal events, such as intermittent ataxia, dystonia, and migraine [9].

The diagnosis of Glut-1 deficiency can be suggested by cerebral spinal fluid hypoglycorrachia in the setting of normoglycemia (CSF glucose < 50 mg/dl or ratio of CSF/serum glucose of < 0.60) or by reduced erythrocyte glucose uptake studies, and then confirmed by the presence of pathogenic variants of the SCL2A1 gene. Early diagnosis of Glut-1 deficiency syndrome is essential as treatment with the ketogenic diet has been found to ameliorate seizures, dystonia, and many of the associated PMDs. The ketogenic diet causes metabolic changes in the liver resulting in the production of large amounts of ketone bodies during fatty acid oxidation. These ketone bodies are able to travel through the bloodstream and cross the blood-brain barrier to provide an alternative energy source for the neurons that lack adequate glucose stores. More recently, a specific medium odd-chain triglyceride preparation that increases hepatic production of both acetyl-CoA and propionyl-CoA has undergone longitudinal trials. The preparation demonstrated good efficacy for the paroxysmal motor disorders in children with Glut-1 deficiency who do not tolerate a traditional ketogenic diet approach to treatment [10].

Sydenham Chorea—an Autoimmune Disorder

Sydenham chorea (SC) is one of the major Jones criteria for the diagnosis of acute rheumatic fever. Other major criteria include carditis, arthritis, erythema marginatum, and subcutaneous nodules. At least one major criterion, along with evidence of an antecedent group A streptococcal infection, is necessary to justify the diagnosis of acute rheumatic fever [11]. The diagnosis of SC is suggested by the insidious onset and worsening of balance and emotional lability over a week or so, followed by more obvious choreiform movements. Most affected children have evidence of a recent group A β -hemolytic streptococcal (GABHS) infection based on the presence of elevated serum antistreptolysin O or anti-DNase B antibody titers. However, up to 25% of patients with SC are serologically negative. Throat cultures for GABHS are rarely positive at the time of onset of SC. However, anywhere from 40 to 75% of children who have SC will have evidence of carditis [12]. As such, it is imperative to screen for carditis in any child with a new-onset of chorea even if seronegative for prior GABHS infection.

In addition to the chorea, hypotonia, and dysarthria, various behavioral disturbances, including impulsivity, passivity, aggression, and obsessive-compulsive behaviors are commonly seen in children with SC. SC's natural course is that of waxing and waning symptoms over weeks to months that ultimately resolve, though behavioral manifestations may persist for more extended periods. Relapses can occur with or without GABHS infection and may be triggered by a viral illness,

pregnancy (chorea gravidarum), or by the use of oral contraceptives.

Apart from the long-term use of penicillin to reduce the risk of recurrent carditis, treatment of SC depends on the severity of the symptoms, with milder cases not warranting any specific intervention for the chorea, which is self-limited. Although reported mostly in uncontrolled cases, treatment with carbamazepine or valproic acid has been reported to improve chorea for more functionally impaired children [13]. Additionally, these medications may be better tolerated than traditional neuroleptics. Benzodiazepines may also be helpful. The use of immune-modulating interventions such as steroids, IVIg, or plasmapheresis is controversial as there are no long-term, placebo-controlled trials documenting their benefits [14, 15].

Neurodegeneration with Brain Iron Accumulation—a Neurodegenerative Disorder

The diagnosis of neurodegeneration with brain iron accumulation (NBIA) includes at least 11 different disorders defined pathologically by the excessive deposition of iron within the basal ganglia and clinically by a progressive extrapyramidal syndrome. Historically, pantothenate kinase-associated neurodegeneration (PKAN) was the first to be discovered and characterized by Julius Hallervorden and Hugo Spatz. They had their names removed from this disorder due to their ties to Nazi Germany in the 1920s and their unethical experiments on Jewish children. A list of the various NBIA disorders, genetic etiologies, genetic inheritance, and distinguishing MRI findings can be found in Table 1.

With NBIAs, there is the symmetric distribution of excess iron accumulation in the globus pallidus with or without other gray matter nuclei involvement. Both calcium and iron appear isointense on T1-weighted and hypointense on T2-weight imaging. CT imaging distinguishes these mineral depositions as calcium appears hyperdense on CT, whereas iron does not. Some radiographic distinguishing “signs” include the “eye of the tiger sign,” the “cortical pencil sign,” and the “halo sign.” The “eye of the tiger” sign is the most recognized sign in NBIA and can be found in PKAN as well as in COASY protein-associated neurodegeneration (CoPAN). The “eye of the tiger sign” is caused by the T2-weighted hypointensity of the globus pallidus with a central anteromedial region of T2-weighted hyperintensity. Histopathologically, the “eye” represents a central rarefaction surrounded by iron-laden neuropil, neurons, and astrocytes. The “cortical pencil sign” is found in neuroferritinopathy (NBIA 3) and consists of iron deposition within the cortical gray matter, which manifests as hypointense T2-weighted signal lining the cortical gray matter. The “halo sign” may be seen with β -propeller protein-associated neurodegeneration (BPAN). It consists of a T1-weighted hyperintensity signal within the substantia nigra

Table 1 NBIA subtypes, genetic etiology, and radiographic features

NBIA subtype	Genetic etiology (inheritance pattern)	*Iron deposition †MRI features
NBIA 1 (PKAN) pantothenate kinase–associated neurodegeneration	PANK2 20p13 (AR)	*GP †“Eye of the tiger sign”
NBIA 2 (PLAN) phospholipase-associated neurodegeneration	PLAG26 22q13.1 (AR)	*GP > SN †Cerebellar and cortical atrophy, thin corpus callosum
NBIA 2a infantile neuroaxonal dystrophy (INAD)		
NBIA 2b atypical infantile neuroaxonal dystrophy (aINAD), (Karak syndrome)		
NBIA 3 (NFT) neuroferritinopathy	FTL1 19q13.33 (AD)	*GP, putamen, dentate †“Cortical pencil sign”
NBIA 4 (MPAN) mitochondrial membrane protein–associated neurodegeneration	C19orf12 19q12 (AD)	*GP and SN †Hyperintense streaking of medial lamina of GP
NBIA 5 (BPAN) β propeller protein–associated neurodegeneration	WDR45 Xp11.23 (X-linked dominant)	*GP and SN †“Halo sign” in the SN; cerebral and cerebellar atrophy
NBIA 6 (CoPAN) COASY protein–associated neurodegeneration	COASY 17q21.2 (AR)	*GP †“Eye of the tiger sign” hypointense SN and GP; swelling of caudate and putamen
Aceruloplasminemia	Ceruloplasmin 3q24–q25 (AR)	*GP, caudate, putamen, thalamus red nucleus and dentate †Cerebellar atrophy
Fatty acid dehydroxylase–associated neurodegeneration (FAHN), (SPG35)	Fatty acid 2-hydroxylase (FA2H) 16q23. (AR)	*GP > SN †Subcortical and periventricular WM T2-hyperintensity
Woodhouse–Sataki syndrome	DCAF (C2orf37) 2q31 (AR)	*GP †Periventricular WM T2-hyperintensity
Kufor–Rakeb disease (PARK 9)	ATP13A2 1p36.13 (AR)	*GP, caudate, and putamen †Atrophy of cerebrum, cerebellum, brainstem, and pyramids

NBIA disorders, associated genes, inheritance pattern, and MRI neuroimaging findings

AD = autosomal dominant; AR = autosomal recessive; GP = globus pallidus; GPi = globus pallidus pars interna; SN = substantia nigra; WM = white matter

and a central band of T1-weighted hypointensity. Other neuroimaging findings such as brainstem, cerebellar, or cortical atrophy with or without subcortical white matter T2-weighted hyperintensities may help to distinguish the various NBIA's further radiographically. Clinically, overlapping phenotypes among the NBIA's as well as with other diseases, differing phenotypes within a single NBIA, and their relatively low prevalence (< 1/1000,000) make diagnosis challenging.

Management of patients with NBIA requires a multidisciplinary approach [16]. Medical therapy for dystonia with trihexyphenidyl and spasticity management with benzodiazepines and baclofen provides variable benefits. Botulinum toxin injections may be useful for oromandibular dystonia, and salivary gland injections can help to reduce sialorrhea. Parkinsonism in PKAN is not levodopa responsive, though it may be beneficial for phospholipase-associated neurodegeneration (PLAN) with the atypical infantile neuroaxonal dystrophy subtype, which has a dystonia-parkinsonism phenotype (Karak syndrome), mitochondrial membrane protein–associated neurodegeneration (MPAN), β -propeller protein–

associated neurodegeneration (BPAN), or Kufor–Rakeb disease (PARK 9). However, it is noted that although the response to levodopa therapy is initially favorable, later onset of disabling dyskinesias and hallucinations are common and prominent in these patients. Intrathecal baclofen therapy has been reported to benefit spasticity and dystonia associated with PKAN in several patients. Deep brain stimulation of the globus pallidus pars interna in PKAN patients has been reported to help significantly with life-threatening dystonic storms. Deferiprone, an oral iron chelator, has been studied in a prospective blinded trial for patients with PKAN. Although there was a significant reduction in the amount of iron within the globus pallidus visualized on MRI after 18 months, and a slowing of worsening of dystonia on the Barry–Albright Dystonia scale (which was not statistically significant), the reported Global Impression of Improvement did not change between deferiprone-treated and placebo-treated patients [17]. Other, nonblinded prospective trials using deferiprone have suggested improvements in the amount of brain iron accumulation seen on MRI as well as

functional improvements on the Unified Parkinson's Disease Rating Scale (UPDRS/III-Motor Section) and the Burke–Fahn–Marsden (BFM) scale for dystonia [18].

Cerebral Palsy

Cerebral Palsy (CP) is the most common movement disorder in children, occurring in 2 to 3 of every 1000 live births. Prematurity and low birth weight are major risk factors for CP [19]. Although birth asphyxia is uncommon, it may be associated with the dyskinetic CP subtypes [20]. Although there is a significant ongoing debate about the definition of cerebral palsy, the current definition states, “Cerebral Palsy describes a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to nonprogressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and/or by a seizure disorder” [21]. The diagnosis of CP encompasses a heterogeneous group of etiologies with a wide variation in clinical presentation. Patients with CP demonstrate several movement disorders with the commonality that they are caused by static injury to the developing brain. The definitive diagnosis can only be made after a period of observation with no progression of symptoms. If there is a deterioration of function over time, one must consider an alternative diagnosis.

There are disorders that are mimics of cerebral palsy, especially early in the course. A strong indicator for a more comprehensive evaluation occurs when there are inconsistencies with the diagnosis of CP. These include normal imaging, signs of regression, absence of risk factors, and a waxing and waning course. At that point, metabolic and genetic testing is appropriate. Comparative genomic hybridization (CGH) microarray is considered the first step in evaluating a patient for possible genetic abnormalities. This technique is effective in displaying chromosomal microdeletions and duplications. CGH is estimated to detect abnormalities in 7–17% of patients with cerebral palsy. If the initial testing is not revealing, then multigene panels and whole exome or genome sequencing is applicable. Evidence now indicates that overall a genetic etiology is present in up to 1/3 of all children with cerebral palsy. [22]. Examples of disorders that masquerade as cerebral palsy include dopa-responsive dystonia, ADCY5, and Glut-1 deficiency [23].

A major consideration in a patient with no causal history is Dopa-responsive dystonia (DRD), DYT 5, or hereditary progressive dystonia with diurnal variation. The disorder is characterized by its responsiveness to levodopa, and also, in some patients, there is a diurnal variation and mild Parkinson features. Clinically this is potentially a very treatable disorder,

and as a result, many advocate to challenge patients with dopa when no etiology for their increased tone can be identified.

Patients with dopa-responsive dystonia have a genetic defect resulting in pathologically in striatal dopamine deficiency with the preservation of striatal nigral terminals. It is known that dopa is produced from tyrosine by the action of tyrosine hydroxylase uses tetrahydrobiopterin (BH4) as a cofactor. BH4 is also a cofactor for tryptophan and serotonin synthesis. Guanosine triphosphate cyclohydrolase (GCH) is the first rate-limiting step for BH4 synthesis. Multiple abnormalities in this metabolic pathway have been recognized to cause autosomal dominant DRD. The common denominator is the inability to manufacture dopa.

The incidence is estimated to be 5 to 10% of patients with dystonia. The classic presentation onset is in the first decade of life but may range from 9 months to 16 years, and late-onset has been documented into the sixth decade. The patient typically develops an abnormal gait with exaggeration of deep tendon reflexes, ankle clonus, and in some patients, extensor plantar responses with a striatal toe. Twenty-five percent of the cases present with a stiff scissoring gait with hyperreflexia and thus are frequently confused with cerebral palsy. The movement disorder expands to all limbs in the first 10 to 15 years with increasing dystonic tone.

Treatment

Small doses of L-dopa at 1 to 3 mg/kg/day or ¼ of a 25/100 mg tablet two to three times a day is a reasonable beginning dose. There have been benefits known to range from 25 to 500 mg/day of L-dopa. Patients are typically responsive in days but may require weeks or longer. If no response to the adjusted dose of the 25/100 tablet three times a day over for several weeks, then the thought is that this is probably a non-responsive patient and excludes the diagnosis. Side effects may include dyskinesia, nausea, and hallucinations. Another medication that may be helpful is trihexyphenidyl.

Prognostically, there are two forms of the disorder: one group of patients has a dramatic response within 1 to 2 days, and others show a slow and less dramatic response, especially with long-standing disease. Overall, there is a good prognosis when patients receive adequate and early treatment [24].

Another mimic of cerebral palsy is ADCY5-related dyskinesia. This disorder has its onset in childhood and as early as infancy with the presentation of hypotonia and delayed milestones. It is characterized by a broad spectrum of fluctuating findings from dystonia, chorea, myoclonus, hypotonia, and spasms to sleep abnormalities. The movement type, episodic or continuous nature, and severity vary within the family and even in the individual. Uniform characteristics include that the hyperkinesia often interferes with function, and cognition is typically spared. Diagnostically, imaging with brain magnetic

resonance imaging (MRI) is typically normal. Genetic confirmation is required [25].

There are limited studies addressing therapy, with some reporting a positive response to clonazepam or clobazam [25]. Deep brain stimulation has been utilized in the circumstance in which medication was not effective. In a study of one adult and two children, the deep brain stimulation did show evidence of improvement in the hyperkinetic symptoms [26].

As an upper motor neuron disorder, patients with CP demonstrate both positive and negative symptoms. The positive symptoms include muscle overactivity and increased flexor reflexes, whereas the negative ones are weakness and loss of fine motor dexterity. In general, only the positive symptoms are amenable to pharmacologic therapy. Unfortunately, the negative symptoms may have a more significant impact on patient function.

Cerebral palsy may be classified by motor abnormalities, associated impairments, and anatomic and radiologic findings, as well as by causation and timing. CP has most commonly been classified into “spastic” or “dyskinetic” subtypes based on the predominant tone abnormalities and movement disorders present. Dyskinetic CP is divided into dystonic and choreoathetoid forms. A small subset of patients may be classified as ataxic. There is inconsistency regarding the use of these terms, and as a result, a patient may be classified differently by different clinicians [27]. Clarification of terms is a priority for furthering research and treatment. Classification by anatomic distribution is based on affected body regions and may include bulbar or trunk involvement as well as descriptions of limb involvement (Table 2) [28]. Motor abnormalities are best described using functional scales.

Management of Muscle Overactivity in Children with Cerebral Palsy

The goal of treating muscle overactivity in patients with CP is to improve function or care and comfort and to prevent future musculoskeletal complications such as contracture and joint subluxation. Thus, treatment must begin with a comprehensive

evaluation by a team of professionals who develop a complete picture of the child in the home and school environment. Although the reduction of muscle overactivity is important, it is only one aspect of the overall treatment plan.

Physical and Occupational Therapy

The therapy program goals include helping the patient develop strength, maintain range of motion, improve coordination, and improve the functions of daily living. The goal is best accomplished while engaging the child in activities they enjoy. Constraint-induced therapy (CIT) is an older technique used for children with hemiplegia. The current resurgence is based on a deeper understanding of the brain’s plasticity, adult stroke patients’ results, and the growing evidence in pediatric patients [29]. The basic technique is to prevent the patient from using the “good” upper limb by constraining its movement and requiring the affected extremity to perform functional tasks. It is widely recognized that children with CP are often weak. Surprisingly, however, the benefits of strength training are much less appreciated. Not only is strengthening helpful, but there are also potential psychological benefits [30].

Oral Medications

The principal oral medications used in the treatment of CP patients are benzodiazepines, baclofen, tizanidine, dantrolene sodium, and gabapentin. The associated sedation and drowsiness often limit their use in children. Many of the trials supporting the efficacy of these agents date back more than 30 years.

- Benzodiazepines facilitate transmission at GABA-A receptors, one of the principal types of inhibitory synapses in the central nervous system. This action results in increased inhibition and reduces mono- and polysynaptic transmission [31]. Diazepam is the most commonly used agent and has been shown to reduce muscle overactivity [32]. One trial of clonazepam has also shown antispasticity efficacy in the CP population [33]. The recommended daily dosage of diazepam is 0.12 to 0.8 mg per kilo up to the adult maximum. The dosing is divided into three to four doses across the day. Sedation is a well-recognized side effect of benzodiazepines and may limit its use. This side effect may be utilized as an advantage when used as a sleep aid.
- Baclofen is a GABA-B agonist recognized as effective for spasticity in adult spinal cord injury. Limited studies address the use of oral baclofen in childhood. In a double-blind crossover trial, baclofen was found to reduce spasticity and allow more passive and active movements [34]. Functional improvement has been more challenging to establish. Side effects with the use of baclofen include

Table 2 Classification of movement disorders in cerebral palsy

Spastic	Diplegia: legs more involved than arms
	Quadriplegia: all four extremities equally involved
	Hemiplegia: one-sided involvement, usually arm more than leg
	Double hemiplegia: arms involved more than legs, usually asymmetrical
Dyskinetic	Hyperkinetic or choreoathetoid
	Dystonic
Ataxic	
Mixed	

confusion and sedation. The sedation does improve over time. The initial dose is traditionally 2.5 mg per day and is gradually increased up to a maximum of 20 to 60 mg per day [35]. A pharmacokinetic study suggested a therapeutic dose of 2 mg/kg for children over 2 years of age [34]. The FDA approval is for 12 years or older.

An important note is that baclofen, whether oral or intrathecal, must be weaned slowly to avoid the withdrawal syndrome. Symptoms of withdrawal include increased spasticity, irritability, mental confusion, and possibly seizures [36].

- Tizanidine is a centrally acting α -2 adrenergic agonist, which prevents the release of excitatory amino acids from spinal interneurons resulting in presynaptic inhibition. As with many medications, the trials of tizanidine in children are limited. One study found tizanidine superior to oral baclofen as an adjunct to botulinum toxin A injections in the gastrocnemius [37].

The dosing recommendations for over the age of 2 years are 0.3 mg–0.5 mg/kg/day divided tid to qid. The maximum dose is 24 mg per day. Due to tizanidine's short half-life, frequent dosing is required. There is frequently accompanying sedation. Although this has been a limiting factor for adults' use, the sedating quality can be an asset in patients with difficulties with sleep initiation. The overall safety of tizanidine is encouraging [38].

- Dantrolene sodium acts at the muscle, reducing calcium efflux from the sarcoplasmic reticulum, thereby decoupling excitation and contraction. There have been variable treatment results in the limited studies published. Spasticity was reduced in two double-blind, crossover studies [39, 40], whereas in a separate placebo-controlled study, a similar effect was not found [41]. Beginning at 5 years of age, the pediatric dosing is recommended to begin at a low dose of 0.5 mg/kg/dose and to gradually increase on a weekly basis to the recommended dose of 6–8 mg/kg/day divided tid or qid. The maximum dose is 100 mg po qid. The lowest effective dose should be utilized.

Although unexpected in medication with a primary peripheral mode of action, sedation, and generalized weakness can occur. Even more importantly, hepatotoxicity is a significant risk factor for adults and is considered a potential risk for children as well.

- Gabapentin's action is thought to be related to the binding of voltage-dependent calcium channels. Gabapentin has more recently been shown to an effective therapy for severe dystonia in nonambulatory children [42]. Gabapentin has more recently been shown to an effective therapy for severe dystonia in nonambulatory children, although it does not have an FDA indication for this use. There was significant functional improvement based on the WHO International Classification of Functioning, Disability,

and Health, Children & Youth version (ICF-CY) [42]. The dosage required is higher than that used in pain treatment. General guidelines based on gabapentin's use in partial seizures ranges up to 25–30 mg/kg per day divided tid. The beginning dose is lower at 10 mg/kg/day. For 12 years and older, the adult dosing is utilized. The medication is advanced in steps, depending on response and side effects. Common side effects include somnolence and dizziness. Behavioral disturbance has been noted in the pediatric age group.

Botulinum Toxin and Phenol Injections

A major advance in the treatment of CP was the introduction of botulinum neurotoxin (BoNT) to treat focal muscle overactivity. For several decades before the use of BoNT injections, phenol, or ethyl, alcohol was used to treat spasticity. The advantage of BoNT is its highly predictable muscle-weakening effect *versus* the somewhat less predictable results, potential side effects, and the procedural difficulty of the other two agents.

The proteolytic enzymes' action in all seven naturally occurring botulinum toxin serotypes is the targeting of acetylcholine vesicle fusion at the neuromuscular junction. Muscle weakness and relaxation occurs because of the loss of acetylcholine release at the neuromuscular junction. In the USA, serotype A is commercially available as Botox®, Dysport®, and Xeomin®. Serotype B is marketed as Myobloc®. The products differ substantially, and therefore, there are no simple dose-conversion ratios among the various marketed products. The serotypes differ in their molecular targets, unit potency, side effect profile, duration of action, and immunogenic potential. Because of these differences, it is critical to recognize the specific product and its proper dosing. This is very important clinically and also when interpreting the literature.

An appropriate candidate for BoNT injection is one for whom the weakening of a limited number of muscles has the potential to provide meaningful benefit in care, comfort, or active function. BoNT may be used in combination with other treatments, such as oral medications or intrathecal baclofen, to provide focal tone reduction. BoNT is injected directly into the overactive muscles. Electromyography, electrical stimulation, or sonography is recommended to provide increased accuracy of injections. Clinical benefit is usually seen within several days, and the peak benefit occurs at approximately 4–6 weeks [43]. The clinical efficacy gradually declines over time, leading to the need for reinjection at 3–4+ months.

Dosing recommendations for BoNT-A have been developed mostly by experience and consensus. Now, there are multiple studies, including double-blind placebo-controlled studies, as well as experience in other countries that have

helped direct the recommended dosage ranges for the products. It is essential to recognize that dosing must be individualized. Multiple parameters are considered, including the child's weight, muscle bulk, degree of spasticity, and prior surgery and response to therapy. The goal is to use the lowest effective dose and an injection interval of at least 3 months to minimize the risk of antibody formation. Because of the very short time frame required for the procedure, most children tolerate the injections with distraction techniques and topical anesthetics. There are circumstances in which the child may need anxiolytics or sedation.

The upper motor syndrome and pattern of spasticity inform the individual muscles and muscle groups injected. For example, the adductors, hamstrings, and gastrocnemius in the lower extremities are the most common. In the upper extremity, the arm and wrist flexors are the most often involved. This is consistent with the adult patient's distributions of spasticity.

Multiple clinical trials of BONT-A have documented the medication's ability to reduce spasticity. Botulinum toxin A has been shown in well over 100 studies to effectively manage focal spasticity in both the upper and lower extremities in patients who have cerebral palsy. The studies have documented spasticity was significantly reduced even at 3 months after injection [44]. Importantly, functional improvements after BoNT injection have also been demonstrated in the lower [45–47] and upper extremities [48]. BoNT has also been used to reduce pain [49].

The FDA has recently approved two of the products, abobotulinum toxinA and onabotulinum toxinA, to treat upper and lower limb spasticity in childhood. The studies were large, multicenter, double-blind, placebo, or low-dose controlled studies. One of the studies of pediatric spasticity in equinus foot deformity in cerebral palsy has been published and documented a significant improvement in both spasticity and function [45]. Other studies that lead to the approvals are currently in press.

From a side effect profile, it was recognized in postmarketing reports that medication effects may spread to areas distant from the injection site. Symptoms include generalized muscle weakness, vision difficulties, ptosis, swallowing problems, urinary incontinence, and respiratory compromise. The time course is hours to weeks after injections, and in some rare cases, have been life-threatening or associated with patient death. Although the reported serious adverse events occurred in adults and children, the risk is thought to be greatest in children treated for significant spasticity. This is due to the presence of comorbid conditions. The FDA implemented a black box warning for all forms of botulinum toxin to address these concerns. However, overall, BoNT-A does have a good safety profile based on multiple studies over the 30 years of use. There is discomfort at the time of injection, but the adverse effects of BoNT injections are usually mild and transient [50–52].

Intrathecal Baclofen

Delivering baclofen into the intrathecal space dramatically lowers the dose requirement by placing the medication in the direct proximity of overactive spinal synaptic connections. Avoiding the enteral systemic route significantly reduces the cognitive side effects [53]. Baclofen is delivered to the intrathecal space via a pump implanted subcutaneously in the abdomen and a catheter inserted in the intrathecal space at the T11-T12 level. The pump is remotely programmable for up to ten dosing parameters via telemetry. The appropriate candidate for intrathecal baclofen (ITB) has significant multisegmental muscle overactivity.

ITB's controlled clinical trials indicate its ability to reduce muscle overactivity and improve function over prolonged treatment periods [53–55]. Potential benefits include reduced spasticity and thus improved burden of care, transfers, and reduced pain. The effects on ambulation may be unpredictable. ITB may reduce the need for orthopedic surgeries to the lower limbs [56]. ITB therapy does carry the risk for complications, including infection, pump malfunction, catheter kinking, and, importantly, medication overdose and withdrawal [57].

Selective Dorsal Rhizotomy

Selective dorsal rhizotomy (SDR) is accomplished by severing overactive dorsal nerve rootlets, which reduces aberrant afferent activity from muscle spindles and results in reduced spasticity. A lumbar laminectomy or laminoplasty is performed, and classically the individual nerve rootlets from L4 or L5 to S1 are stimulated. Those rootlets resulting in excessive muscle activity are severed. Typically, 25 to 60% of nerve rootlets are severed [58].

Multiple controlled trials have demonstrated SDR's ability to reduce lower limb spasticity, increase range of motion self-care, and gait [59, 60]. The best candidates for surgery are children ages 3 to 7, with spastic diplegia, good trunk control, and leg strength, with the ability to isolate leg movements [61]. Intensive postoperative physical therapy is essential to mobilize the patient and regain pre-operative motor function. Scoliosis is a potential long-term side effect of SDR and should be monitored closely.

Orthopedic Surgery

Despite the best management, many children with CP will eventually require orthopedic surgery to correct fixed contracture. The most common surgery sites are the heel cords for equinus or equinovarus, and the most common operation is tendon lengthening with or without transfer. There is optimism that early and comprehensive treatment of muscle overactivity may prevent later complications. Unfortunately,

children with spastic cerebral palsy often require orthopedic surgery to treat secondary deformities (muscle contractures, hip dysplasia, bony deformities). The orthopedic intervention is frequently needed despite diligent therapies and appropriate hypertonia management. Following growth spurts, progressive issues with hamstring contractures and gait disturbances lead to the need for hamstring tenotomies, which are common in adolescent patients with CP. Scoliosis is a significant concern and must be evaluated in children with cerebral palsy. Scoliosis development is most dramatic in GMFCS V patients who have up to a 90% risk for spine deformities [62].

Management of Dystonia and Mixed Movement Disorders

Motor dysfunction in CP is due to a disruption of the complex integration of multiple brain areas, including cortex, cerebellum, basal ganglia, brain stem, and other motor and sensory thalamocortical pathways. Although it is unclear how the lesions lead to dystonia and choreoathetosis, three hypotheses have included the loss of inhibition, sensory dysfunction, and impaired plasticity in the basal ganglia circuits [63].

Mixed movement disorders are now considered more the norm than the exception in patients with cerebral palsy and directly impact treatment success. Hyperkinetic movement disorders are much less responsive to the frequently used interventions described for spasticity.

Dystonia may not be evident early in a patient's life before the age of 3 or 4 years and may develop as late as 12 or 13 years of age. Dystonia may also evolve and progress over time [64]. This progression has apparent implications when considering that interventions performed earlier in life. Dystonia treatment choices are limited. A recent study pointed out the paucity of evidence for oral medications and botulinum toxin but supported that ITB and deep brain stimulation (DBS) are possibly effective [65]. Generally, botulinum toxin is used with clinical success for focal dystonia as well as for spasticity. Often, the indications coincide.

Oral medications for dystonia are often tried but have shown controversial efficacy. Diazepam's clinical efficacy in athetosis is thought to be due to generalized relaxation [66]. An open-label clinical trial of trihexyphenidyl in children with dystonic CP showed some evidence of efficacy in the upper extremities. However, children with hyperkinetic-dystonic movement disorders appeared to have worsening of their dyskinesia [67]. Based on its known action in other movement disorders, L-dopa/carbidopa has been used, though clinical trials in patients with CP are lacking. Levetiracetam has been reported to be helpful in paroxysmal kinesio-genic choreoathetosis [68] and may improve balance and fine motor skills in children with choreoathetosis [68, 69]. Tetrabenazine, a monoamine-depleting medication use in patients with cerebral palsy and associated hyperkinetic movement disorders, has been anecdotal [70]. Gabapentin has been

used in patients with severe dystonia and has shown significant improvement based on the Dystonia Severity Assessment Plan [42]. Oral baclofen is used in hyperkinetic movement disorders with questionable success. However, several studies have reported improvement with intrathecal baclofen. Studies have documented improved comfort and ease of care in patients with generalized secondary dystonia in 85%, and notably, 33% demonstrated functional improvement [71]. The medication's action is hypothesized to be at the cortical level.

Bilateral pallidal deep brain stimulation has also gained interest in children's and adults' care with cerebral palsy and associated dystonia [72, 73]. In a prospective study of adult patients with dystonia-choreoathetoid cerebral palsy, improvements were seen in the Burke-Fahn-Marsden dystonia rating scale as well as disability, pain, and quality of life at 1 year. The posterolateroventral region of the GPi was deemed the optimal target [73]. In a study of children with dystonia of various etiologies, the entire group significantly improved pain frequency and severity as well as analgesia requirements [74].

Summary

In summary, pediatric tone and movement disorders are a challenging and complex set of disorders with multiple disease etiologies, overlapping tone and movement disturbances, and treatment modalities. Most therapeutic interventions are not supported by prospective controlled trials, and treatment is based more on proposed mechanisms of effect. Many medications and interventions are also not approved by the FDA for use in children, which creates its own set of challenges in dosing, safety, and insurance authorization. It is imperative that further research in the management of movement and tone disorders include children and uses age-appropriate functional outcome measures to allow providers the best information to optimize functional capabilities and, ultimately, quality of life for children who suffer from these disorders.

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