Challenging neurological symptoms in paediatric palliative care: An approach to symptom evaluation and management in children with neurological impairment

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Neurological symptoms are very common in children with life-limiting conditions and are challenging in terms of burden of illness. Moreover, neurological symptoms can significantly impact the child's quality of life and contribute to distress among parents, families, caregivers and health care providers. Knowing how to manage and alleviated these symptoms is essential for providing good palliative care. In the present article, the more common neurological symptoms of agitation/irritability, spasticity and dystonia will be reviewed. The aim of the present brief review is to provide a basic approach to both the identification and treatment of these neurological symptoms. A medication table is provided for quick reference. A brief commentary and guidance for the management of pain are also incorporated, with reference to further literature sources.

Key Words: *Agitation; Dystonia; Irritability; Paediatrics; Palliative care; Spasticity*

Des symptômes neurologiques difficiles en soins palliatifs pédiatriques : une conduite pour évaluer et prendre en charge des symptômes chez les enfants ayant une atteinte neurologique

Les symptômes neurologiques sont très courants chez les enfants ayant des problèmes limitant l'espérance de vie, et le fardeau de la maladie est difficile à prendre en charge. De plus, les symptômes neurologiques peuvent avoir des effets marqués sur la qualité de vie de l'enfant et contribuer à la détresse des parents, des familles, des soignants et des dispensateurs de soins. Il est essentiel de savoir comment prendre en charge et soulager ses symptômes pour offrir de bons soins palliatifs. Dans le présent article, les symptômes neurologiques plus courants d'agitation ou d'irritabilité, de spasticité et de dystonie sont abordés. L'analyse qui y est présentée vise à proposer une conduite de base pour déterminer et traiter ces symptômes neurologiques. Un tableau de médicaments facilite la consultation. Un bref commentaire et des conseils sur la prise en charge de la douleur sont également proposés, de même que des références vers d'autres publications.

CASE PRESENTATION

A 22-month-old boy is referred to you for episodic body arching and screaming. The episodes occur daily and cluster, lasting for 5 min to 20 min at a time, with little relief in between. He has not slept well for weeks. His complex medical history includes severe neonatal hypoxic-ischemic encephalopathy, cortical visual impairment, seizures and gastroesophageal reflux; the latter two conditions are being pharmacologically treated. Pain assessment has been performed using the Non-Communicating Children Pain Checklist – Revised (NCCPC-R [1]) to monitor pain intensity, and thorough investigations have ruled out hidden sources of pain (Figure 1). Pain medications, including gabapentin, have been tried to treat the episodes, without significant improvement. During the episodes, he is in significant distress. His entire body arches, he is diaphoretic and cries inconsolably. His vital signs are within normal ranges except for a heart rate of 160 beats/min; he is so irritable that the physical examination is nearly impossible. His parents are distressed; they hope that you can identify a cause for his discomfort and determine a treatment approach that will restore quality of life. How would you assess and treat this young child?

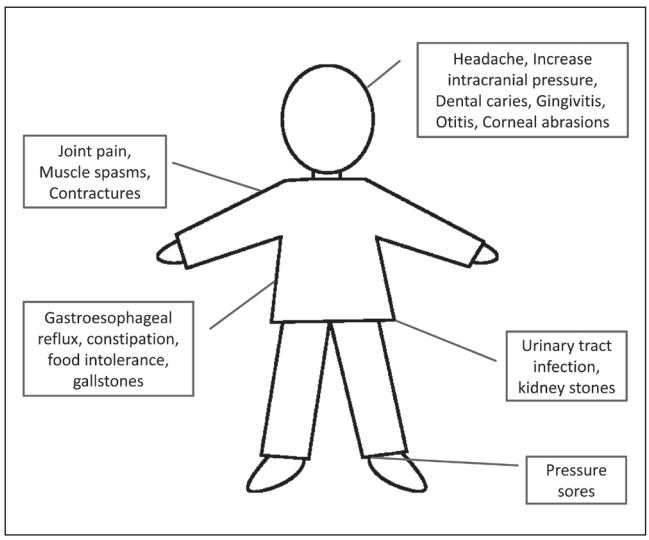

Figure 1) *Sources of hidden pain in children with neurological impairment.*

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TABLE 1
Approach to agitation/irritability

Thought-provoking questions	Elements to consider
Is this agitation/irritability?	• Completing a detailed history and physical examination is essential to: ○ Differentiate between agitation/irritability versus changes in functioning resulting from primary psychiatric illness, encephalopathy and delirium (7)
What are the provoking factors?	• Pain is of key consideration; nociceptive pain (somatic and/or visceral) and neuropathic pain must be considered (Figure 1) • Systemic symptoms can lead to agitation/irritability especially in children with neurological impairment. Dyspnea, nausea and dysautonomia should be considered • Psychological distress should also be considered
Are medications contributing?	• Drug toxicity should be considered and trial discontinuation of specific medications may be indicated

INTRODUCTION

Symptom burden can be high in children with life-limiting conditions, especially those with neurodegenerative conditions and impairment of the central nervous system (2,3). Neurological symptoms are difficult in terms of quality of life for the child, and also contribute significantly to distress among parents, families and health care providers (2,3). Knowing how to manage and alleviated these symptoms is essential for providing good palliative care.

Neurological symptoms are varied and include seizures, agitation/irritability, spasticity/muscle spasms, and movement disorders such as dystonia, chorea and myoclonus. The underlying etiology for these symptoms is generally multifactorial, and overlap of many symptoms at once is common. Beyond identifying the specific symptom at hand, it is also essential to undertake a comprehensive and meticulous exploration of the differential diagnosis to clarify the underlying etiology. That said, exploring the numerous possible etiologies for each neurological symptom is beyond the scope of the present article. Rather, the present article will provide a basic approach for certain neurological symptoms and then focus on management. It will specifically focus on agitation/irritability, spasticity and dystonia.

The present article is aimed toward use by general practitioners and paediatricians. It should be noted that many of these clinical scenarios are highly complex, and involvement of paediatric palliative care specialists and neurologists should be considered. Further consultation with neurosurgery, physiotherapy, occupational therapy, dentistry and psychiatry/psychology may also be considered. Given the challenging nature of these neurological symptoms, working with a collaborative multidisciplinary team is recommended.

GENERAL APPROACH

Several issues specific to the paediatric population need to be considered, the first being the variable age and stage of development. Not only will the expected symptoms differ according to the age and development of a child, but the child's perception of these symptoms and the consequential affect on their quality of life may also vary (4). Furthermore, children with developmental delay and cognitive disability may express and experience symptoms differently (3,4). Second is the uncertainty of the evolution and prognosis for many of the rare neurodegenerative diseases encountered in paediatric palliative care (3). Third, it is important to remember that several neurological symptoms can coincide, as can other 'non-neurological' symptoms such as pain or signs of sepsis. Therefore, it can be very difficult to determine which symptom is the most bothersome and requires treatment. Pain is a notable example because it can both result from and exacerbate neurological symptoms. Although the present article does not focus specifically on pain, identifying and treating any hidden sources of pain should be a priority when caring for a child with challenging neurological symptoms (Figure 1). Finally, there is very little research documenting the incidence, presentation and management of neurological symptoms in paediatric palliative care (3-5). Therefore, one needs to rely on their clinical experience and the experience of their colleagues to help guide management. Often, a time-limited trial of medication is necessary to uncover what symptom is most problematic; frequent reassessments are important with consultation with specialists if the first-line treatments are unsuccessful. New or increased neurological symptoms may indicate a change or progression of a child's condition; it is important to discuss any proposed intervention in the global context of care for the individual child.

As a general approach to neurological symptomatology, we recommend that the first question to ask is, "What is this symptom?". It is essential to obtain as detailed a history as possible. These days, technology can be of great support; asking caregivers to provide a video of an episode can help describe the complex symptomatology. Again, there may be more than one symptom at play, which is important to remember. Once the exact symptoms have been determined, the next question to ask is, "Are there provoking factors and, if so, what are they?". Common provoking factors include pain, dyspnea, infections, constipation, gastroesophageal reflux and dehydration. Asking parents to keep a diary is a useful tool to identify potential triggers. Subsequently, a thorough medication review is necessary, often with the assistance of a pharmacist, to identify medications with potential adverse neurological effects. Once the precise symptoms have been identified, investigated and all provoking factors addressed, targeted treatment must be contemplated and implemented for persistent symptoms.

Agitation/irritability, spasticity and dystonia will now be reviewed in more detail (Tables 1 to 3); for each section, please refer to the attached table for pertinent medication details (Table 4).

AGITATION/IRRITABILITY

According to the Oxford Dictionary, agitation is a state of anxiety or nervous excitement (6). Medically, agitation or irritability is used to describe unpleasant psychological and physical arousal, often in circumstances in which the underlying etiology remains unclear. It refers to a complex set of symptoms and signs that are distressing to the patient, their family and caregivers. Agitation/irritability may consist of psychological symptoms (anxiety, anger, irritability), physical symptoms (restlessness, hypermotor activity, crying, angered speech, disturbed sleep patterns) and autonomic changes (tachycardia, tachypnea, increased blood pressure, diaphoresis) (7,8).

Once agitation/irritability is identified and explored, it is important to treat all underlying provoking factors. If agitation/irritability persists, it is then time for directed symptom management. The first approach is with nonpharmacological interventions such as environmental control (limiting visitors, maintaining a

TABLE 2
Approach to spasticity

Thought-provoking questions	Elements to consider
Is this spasticity?	• Completing a detailed history and physical examination is essential to: ○ Differentiate spasticity from rigidity and dystonia, which require different treatments ○ Differentiate between baseline increased muscle tone (spasticity) and intermittent muscle spasms
What are the provoking factors?	• Spasticity and muscle spasms can worsen in response to pain, fever, infection and other causes of discomfort • Psychological stress and agitation/irritability can increase spasticity
Are medications contributing?	• A medication review is always advisable, although this may be less fruitful in spasticity

TABLE 3
Approach to dystonia

Thought-provoking questions	Elements to consider
Is this dystonia?	• Completing a detailed history and physical examination is essential to: ○ Differentiate dystonia from spasticity and other movement disorders • When in doubt, it is prudent to investigate as if dystonia is present and perhaps even trial a medication • Sometimes it is only with improvement from a trial of medication that the presence of dystonia can be confirmed
What are the provoking factors?	• Dystonia can worsen in response to pain, fever, infection and other causes of discomfort • It is also important to consider anxiety, fear, and other forms of psychological stress, all of which can worsen dystonia
Are medications contributing?	• Several common medications can induce and worsen dystonia, dopamine-receptor blocking agents such as anti-emetics and gastrointestinal promotility agents being common • Dystonia has also been reported with selective serotonin reuptake inhibitors, opioids, methylphenidate, gabapentin, and general anesthesia using propofol or fentanyl (18) • Medication interactions should also be thoroughly explored

tranquil environment), soothing and calming practices (playing music, reading stories), and using available therapies (psychology, play therapy, music therapy) (8). The next step is pharmacological management. There is little direct evidence as to what medications work best for agitation/irritability in paediatrics, but many medications are available (4,7,8).

Agitation/irritability and neuropathic (central) pain can be difficult to delineate because they may represent identical symptomatology. For this reason, neuropathic pain medications should be considered and tried. Gabapentin is a safe first-line treatment due to few medication interactions and very few side effects, although minor temporary sedation is possible (3,9). Pregabalin, a similar medication, is not used as frequently in children because it is only available in tablet form. Many other medications can be used to control neuropathic pain; a complete review is beyond the scope of the present article. We refer the readers to references from Hauer (10) and Siden et al (11).

When dysautonomia is prominent during the episodes, clonidine, an alpha-2-adrenergic receptor agonist, needs to be considered for use on a regular basis and 'as needed' during crisis (10). Other possible agents include gabapentin, opioids and benzodiazepines, the latter two mostly on an 'as needed' basis during autonomic storms (3).

Benzodiazepines, through their action on the $GABA_A$ receptor, can be helpful in treating agitation/irritability for short periods of time; many patients will develop tolerance over time when used regularly. They are readily available in several forms, dosages and durations of action. In the 2008 WHO Essential Medicines List for Children in palliative care, benzodiazepines (diazepam and midazolam) were recommended as essential for management of anxiety and agitation/irritability (4). The main drawback to benzodiazepines is sedation. Increased salivary secretions, respiratory depression and paradoxical reactions (restlessness, confusion, aggressivity, self-injurious behaviours) are also possible, although rare.

Antipsychotic medications are also used in the treatment of agitation/irritability; in fact, haloperidol is listed as an essential medication for treatment of agitation/irritability in the 2008 WHO Essential Medicines List for Children in palliative care (4). The main benefit of the antipsychotic medications is less sedation. The main drawback with these medications is the risk of extrapyramidal symptoms and, for some, a decreased seizure threshold. Most are also not available in suspension, and very little anecdotal data exist about their use buccally (using the intravenous formulation). We recommend consulting a paediatric neurologist or psychiatrist to help manage this class of medication.

In extreme situations when first- and second-line medications are not relieving the agitation/irritability, using a more sedative agent, at least temporarily, may be appropriate. Several medications may be tried including chloral hydrate, dimenhydrinate and methotrimeprazine (7,8). Collaborating with a paediatric palliative care specialist is strongly recommended in those situations.

SPASTICITY

Spasticity is a resistance in muscle tone that increases in a velocity-dependent manner and is associated with hyper-reflexia (12). Spasticity is usually considered to be nonpainful, but it often coexists with intermittent muscle spasms, and subsequently pain and discomfort (3). Spasticity can also lead to considerable difficultly in obtaining functional and comfortable postures for ambulation, sitting and sleeping (13). Over time, spasticity can lead to the development of contractures and deformity, which can feed back into issues with pain, muscle spams and difficult posture (13). Spasticity leads to difficulty with the passive movement needed for caregiving such as toileting, washing, dressing, etc. This can cause pain and discomfort for both the child and their family during activities of daily care (13).

Once spasticity is identified and explored, it is important to treat all underlying provoking factors. Specific treatment for the spasticity should be considered and implemented as required, balancing benefits and side effects. The treatment options include nonpharmacological therapeutics, medications and surgical interventions. Before implementing spasticity treatment, it is important to confirm that the spasticity does not have a functional component. This is most often considered in the setting of an ambulatory child

TABLE 4
Medications for neurological symptoms (references 3, 23-29)

	Starting dose	Maximum dose	Plasma half-life, h	Most common side effects	Drug interactions	Contraindications
Agitation						
Gabapentin	3–12 y: day 1: 5 mg/kg/dose PO at bedtime; day 2: 5 mg/kg/dose PO BID; day 3: 5 mg/kg/dose PO TID. After day 3: titrate every 2–3 days over 2–3 weeks as tolerated. ≥12 y: start at 100 mg TID, titrate to effect with increase of 300 mg/day. Can titrate faster or slower depending on tolerance and pain severity	Children: Usually 35–50 mg/kg/24 h divided in 3 doses. Adults: 3600 mg/day	5–7	Somnolence and fatigue and dizziness early on, tend to improve with time	Wait at least 2 h after antacids	Dose adjustment in renal disease
Clonidine	Day 1–3: 0.002 mg/kg PO at bedtime; day 4–6: 0.002 mg/kg PO BID; day 7–9: 0.002 mg/kg PO TID. Can titrate faster as tolerated	Max starting dose: 0.1 mg (50 kg) Max dose: 0.012 mg/kg/dose (0.6 mg, for 50 kg) TID	5–25	Decreased blood pressure, somnolence	Tricyclics (decrease effect), methylphenidate. Need to be careful with any medications lowering blood pressure or heart rate	Bradyarrhythmia, low blood pressure, galactose intolerance. Need to be careful with renal disease
Diazepam	6 m and older: 0.12–0.8 mg/kg/24 h PO divided 3–4 times/day 0.04–0.3 mg/kg/dose IV every 2–4 h PR route also possible. Cannot be given SC	0.6 mg/kg IV within an 8 h period	24–48	Drowsiness, ataxia, hypotonia, muscle flacidity, paradoxical reaction	Metabolized via Cytochrome P450 group of liver enzymes	Acute/severe pulmonary insufficiency, sleep apnea syndrome, severe liver disease, myasthenia gravis
Midazolam (continuous infusion IV/SC)	Neonatal: 1 µg/kg/min; 1 m–18 y: 50–300 µg/kg/h PO/buccal also possible	6 m–5 y: 6 mg; 6–12 y: 10 mg	2–5	Drowsiness, paradoxical reaction	Other substrates of CYP3A4.	Careful with liver/renal disease
Lorazepam	Infants and children: 0.02–0.1 mg/kg/dose PO/SL/IV/SC every 4–8 h;	2 mg/dose	10–20	Drowsiness, impaired psychomotor skills, lightheadedness, paradoxical reaction	Valproic acid, carbamazepine, rifampin	Mania
Haloperidol	Oral: <12 y: 10–20 µg/kg every 8–12 h; 12–18 y: 1.5 mg 3 times/day IV; 1 m to 12 y: 25–85 µg/kg/24 h; 12–18 y: 1.5–5 mg/24 h		13–35	Extrapyramidal effects, sedation	Carbamazepine (decrease plasma concentration of haloperidol)	Long QT
Dimenhydrinate	Children over 2 years: 5 mg/kg/24 h PO/IV/PR divided q6h; 6–12 years: 25–50 mg/dose PO q6–8 h	75 mg/24 h PO 150 mg/24 h PO 300 mg/24 h IV		Drowsiness, dizziness, paradoxical excitation (younger children)		Glaucoma
Methotrimeprazine	Data for SC – but has been used IV anecdotally. 1–12 y: 0.35–3 mg/kg/24 h; 12–18 y: 12.5–200 mg/24 h		15–>30	Drowsiness, postural hypotension, antimuscarinic effects		Parkinson, epilepsy (in some cases), hypothyroidisn, myasthenia gravis, antihypertensive medications
Chloral hydrate	25–50 mg/kg/24 h PO/PR divided q6–8 h	500 mg/dose	8	Gastric irritation, vomitting; sedation, respiratory depression	Warfarin	Severe renal/hepatic dysfunction
Spasticity						
Diazepam	See above					
Tizanidine	18 m–7 y: 1 mg/day 7–12 y: 2 mg/day; ≥12 y: 2 mg/day	36 mg/day (for ≥12 y)	2.5	Drowsiness, weakness, dry mouth, hypotension, dizziness	Dygoxin or hypotensive drugs,	Long QT, Careful with liver/renal disease

Continued on next page

TABLE 4 – CONTINUED
Medications for neurological symptoms (references 3, 23-29)

	Starting dose	Maximum dose	Plasma half-life, h	Most common side effects	Drug interactions	Contraindications
Baclofen	1–10y: 0.3 mgkg/day in 4 doses; 10–18y: 5 mg 3 times/day	Max initial dose: 2.5 mg/ max 100 mg/day (at maintenant)	3.5	Sedation, drowsiness, hypotonia, nausea, urinary frequency or incontinence, dysuria		Peptic ulceration, severe psychiatric disorders, epilepsy, respiratory impairment, diabetes mellitus, urinary retention, careful with liver/renal disease
Dantrolene	0.5 mg/kg/dose PO once to twice daily	400 mg/24 h	Approximately 9	Drowsiness, dizziness, muscle weakness, diarrhea	Careful with other hepatotoxic drugs	Active hepatic disease
Dystonia						
Diazepam	See above					
Trihexyphenidyl	Average initial dose 0.095 mg/kg/day Adults: 2–5 mg 1–3 times/day			Anticholinergic effects, drowsiness, dizziness	Anticholinergics, cholinesterase inhibitors, potassium chloride	Glaucoma, myasthenia gravis
Benztropine	0.02–0.05 mg/kg/dose IV/PO daily-twice a day	1–4 mg/dose PO/ IV daily – twice a day		Anhidrose, hyperthermia, illeus, gastroesophagial reflux, dry pulmonary secretions	Anticholinergics, cholinesterase inhibitors, potassium chloride	Glaucoma, pyloric or duodenal obstruction, or myasthenia gravis
Nitrazepam	0.3–1 mg/kg/24 h PO divided in 3 doses/day		30	Drowsiness, impaired psychomotor skills, hypotonia, bronchial hypersecretion		Difficulty managing oral secretions, careful with liver/ renal disease
Tetrabenazine	No established paediatric dosing. Adults: 12.5–25 mg 2–3 times/day			Hypotension	CYP2D6 Inhibitors, levodopa, antide-pressants and monoamine oxidase inhibitors, reserpine	Long QT, depression, careful with liver impairment
Carbidopa-levodopa	No established paediatric dosing. Adults: one tablet of 100/25 3 times a day	1500 mg levodopa per day	1.4	Dyskinesias, nausea, mental changes	Antipsychotics, dopamine-depleting agents, iron, methoclopramide, isoniazid	Antihypertension medications (risk of postural hypotension)

The initial dosages may differ according to the specific situation. Always verify dosages with a pharmacist if uncertain. Most medications mentioned should not be stopped abruptly. BID Twice daily; IV Intravenous; m Months of age; PO Per os (orally, nasogastric tube or g-tube); PR Per rectum; TID Three times daily; SC Subcunaneous; SL Sublingual; y Years of age

in which the increased tone may be counteracting underlying weakness (8,13). At times, spasticity also supports the seated position of the child, so this needs to be carefully considered.

Nonpharmacological treatment options for spasticity include physiotherapy, adjustments to their environment and activities of daily living by occupational therapy, as well as efforts provided by caregivers such as stretching exercises and massage (14). Pharmacological treatments generally include either enteral medication for generalized spasticity or injection medications for alleviation of more localized spasticity (13-15). Common enteral medications include benzodiazepines (diazepam), alpha-2 adrenergic agonists (tizanidine), GABA-receptor agonists (baclofen) and muscular calcium-blockers (dantrolene) (13-15). According to the American Academy of Neurology practice guideline, there are level B data for diazepam as a short-term treatment (caution regarding toxicity), level C data for tizanidine which may be considered, and insufficient data for the others (13). That said, clinical experience indicates that baclofen is often used as a first-line treatment in many centres. Botulinum toxin A is administered by injection for localized spasticity (13-15). For this use, botulinum toxin A is considered to be safe and efficacious, with level A data (13). Phenol is another injection medication, but the evidence for its use is insufficient according to the American Academy of Neurology practice parameter (13,15).

Neurosurgical and orthopedic interventions are available for the management of spasticity, such as muscle lengthening, tendon release, intrathecal baclofen, selective dorsal rhizotomy, etc (14,16,17). These procedures are typically not initiated during end-of-life, but may be of benefit in specific circumstances during the broader palliative care context (management of life-limiting conditions).

DYSTONIA

Dystonia is a hyperkinetic involuntary movement disorder in which sustained or intermittent contraction of both agonist and antagonist muscles results in repetitive movements, twisting and unnatural positioning of the body (12). Dystonia commonly affects the limbs, but it can also involve the muscles of the trunk, cervical region and even the facial (oral) musculature. For the purpose of the present article, the most important classification is between generalized dystonia and focal dystonia, a distinction that determines the treatment approach (enteral medication versus localized injection). Dystonia can be extremely painful and lead to significant difficulties for both self-care and caregiving by others. Thus, dystonia can be particularly difficult in terms of its impact on the child's activities of daily living and quality of life.

Once underlying provoking factors and medication have been appropriately addressed, the next step is pharmacological treatment. It is important to remember that the benefit may be incomplete or accompanied by significant and intolerable side effects; thus, medicating for dystonia is only recommended if the symptom is truly leading to significant pain and/or burden on the child's quality of life.

Pharmacological treatment includes both enteral and injection routes. Among enteral medications, anticholinergic treatment is the most common (19,20). The efficacy and tolerability of anticholinergic medications (trihexyphenidyl and benztropine) for dystonia in children is poorly documented and, therefore, physicians must proceed with caution, starting with small dosages and increasing slowly as needed, balancing benefit and side effects. It is essential to understand the potential side effects of anticholinergic and monitor appropriately; this includes reduced diaphoresis (increased body temperature), dilated pupils, decreased bodily fluids (dry mouth, dry eyes), erythema of the skin and confusion/delirium (20). Other enteral medications that can be considered for dystonia (with less evidence) are benzodiazepines (diazepam, nitrazepam), GABA-receptor agonists (baclofen) and dopamine-depleting agents (tetrabenazine) (19-21). Drugs ordinarily reserved for dopamine-responsive dystonia (carbidopa-levedopa) may also be considered and trialed in specific situations, in consultation with a neurologist (19,20). Finally, botulinum toxin A injection is the treatment of choice for most types of focal dystonia (19,20). Clinical experience indicates that anticholinergic medications and tetrabenazine are first-line treatments; that said, dystonia is a complex symptom and often very delicate to manage appropriately. Therefore, consultation with a neurologist and/or a formal referral to neurology is recommended before initiating treatment for dystonia.

Neurosurgical approaches, including deep-brain stimulation of the globus pallidum internum, are well established for treatment of dystonia; however, these would be considered to be extreme and invasive measures in a palliative setting (19,20,22).

CONCLUSIONS

Clinical scenarios, such as that described at the beginning of the present article, are not only distressing for patients and families, but they are also challenging for health care teams. Neurological symptoms often present in children that are medically complex, and these symptoms can be particularly difficult to assess and treat effectively. Distinguishing among different neurological symptoms requires a detailed history and careful verification of all potential triggering factors. Pain, either nociceptive or neuropathic, needs to be meticulously explored and treated. Management includes nonpharmacological therapeutics endeavors and medications, as well as consideration of surgical procedures in intractable situations. Collaborative and interdisciplinary teamwork is strongly recommended in the management of children with complex neurological symptomatology. As noted in the medication table, specific recommendations for paediatric dosing are too often lacking. Not only is further focused pediatric palliative care research needed, but publications on clinical experience are required as well. Local expertise, once captured and reviewed at a national level, becomes relevant and helpful to other clinicians.

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