Supportive and palliative care of children with metabolic and neurological diseases

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Purpose of review
To review the role of pediatric palliative care (PPC) for children with metabolic and neurological diseases.

Recent findings
There is a growing body of literature in PPC, though it remains limited for children with metabolic and neurological diseases. Evidence indicates the benefit of PPC. Utilization of PPC programmes can facilitate communication, ensure that families are better informed, improve certainty with decisions, enhance positive emotions, result in fewer invasive interventions at the end of life, and have an impact on location of death. Barriers to utilization of PPC include concern about taking away hope and uncertainty about prognosis. Challenging areas for children with metabolic and neurological diseases include the identification of distressing symptoms and prognostic uncertainty. This article aims to review literature relevant to this group of children, as well as provide a framework when considering specific palliative care needs.

Summary
PPC for children with metabolic and neurological diseases can lessen a child's physical discomfort and enhance parental certainty with decision-making. These areas along with other needs throughout the illness trajectory and bereavement are being increasingly met by the growing availability of PPC programmes.

Keywords
decision-making, metabolic disease, neurological impairment, pediatric palliative care

INTRODUCTION

Pediatric palliative care (PPC) intends to relieve suffering of the child and family, (physical, emotional, and spiritual), improve the child's quality of life, provide support through illness and bereavement, assist with coordination of care, and facilitate decision-making [1▪▪]. PPC includes the provision of concurrent care along with curative therapy, and is considered best implemented at the time of diagnosis.

There is increasing availability of PPC. Of the 72% responders of 226 hospitals surveyed, as identified by the National Association of Children's Hospitals and Related Institutions, 69% reported having a PPC programme [2▪]. Many programmes are restricted to inpatient services because of limited resources. The two most common principal diagnoses in a PPC multicenter cohort study were 41% genetic or congenital disorders and 39% neuromuscular disorders [3]. The most common reasons for palliative care consults in this study were to assist with symptom management, communication, and to facilitate decision-making [3]. The most common goals that parents identify as part of decision-making include comfort, quality of life, avoidance of suffering, and to maintain or improve health [4,5]. Parents also value facilitation of shared decision-making [6].

This article will focus on impairment of the central nervous system (CNS) as a common unifying characteristic of children with metabolic and neurological diseases. Although metabolic diseases can involve other organs, the involvement of the CNS is the most common source of many distressing symptoms and life-threatening events [7,8▪,9]. In this article, this group will be referred to as children with neurological impairment.

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KEY POINTS

- There is increasing availability of PPC programmes to meet the complex needs of children with metabolic and neurological diseases, along with the needs of family members.
- Unique challenges include identification of pain in children who remain nonverbal throughout life.
- Prognostic uncertainty can increase the risk of invasive testing and interventions at the end of life; this can be lessened by the utilization of PPC.
- Other benefits to PPC for this group of children include improved symptom management and decreased hospital length of stay.

BENEFITS TO PEDIATRIC PALLIATIVE CARE AND ADVANCE CARE PLANNING

Literature consistently indicates the benefit of PPC. Utilization of PPC programmes can enhance positive emotions, facilitate communication, ensure that families are better informed, improve certainty with decisions, and have an impact on location of death [10]. The fear that PPC increases distress is unjustified. PPC can also decrease the use of aggressive interventions at the end of life. A retrospective cohort study identified that the provision of PPC resulted in significantly fewer invasive interventions at the end of life, including the use of mechanical ventilation or surgical procedures, as well as fewer admissions to the ICU and fewer deaths in the ICU [11▪▪]. Other areas of identified benefit from PPC include psychological support, quality of life improvement, and symptom control [12].

BARRIERS TO PEDIATRIC PALLIATIVE CARE

Although there is increasing recognition to the benefits of PPC, there continues to be barriers to its utilization, including the inherent prognostic uncertainty that exists in pediatrics. Examples of barriers identified as interfering with the initiation of advance care discussions (ACDs) included clinician' concern about taking away hope, clinician uncertainty about prognosis, and clinicians not knowing the right time to address the issues [13▪▪]. Factors perceived from parents included unrealistic parent expectations, differences between clinician and patient/parent understanding of prognosis, and lack of parent readiness to have the discussion. The majority (92%) of respondents believed that a discussion regarding overall goals of care is ideally initiated upon diagnosis or during a period of stability. However, 60% reported that these discussions typically take place during an acute illness or when death is clearly imminent, and less than one-third of clinicians believed that ACD typically happen at the right time in the course of the illness [13▪▪]. A review of a newly developed PPC programme identified that the most common reasons physicians decided against obtaining a PPC consult included 'family not ready for palliative care' and 'unclear of palliative care benefits [14].'

UNIQUE THEMES FOR CHILDREN WITH METABOLIC AND NEUROLOGICAL DISEASES

This section aims to identify themes and challenges relevant to children with neurological impairment and their families, opportunities for future study to determine how these barriers impact the introduction of palliative care, and how parental decision-making is supported. For most conditions that result in neurological impairment, cure is not possible, rather interventions intend to modify the disease trajectory. Times of stability are punctuated by acute health decline and recovery, often to a new plateau, with uncertainty of this trajectory creating uneasiness for families [15]. It is often not possible to know when the next acute health exacerbation will be life-threatening. Overall decline in health can occur slowly, often over months to years. Families encounter the challenges of providing complex intense care that becomes the new normal, the duality of joy and sorrow, and the uncertainty of when the next acute event will occur [15]. Other challenges include the difficulty with identifying the presence of pain, dyspnea, and other distressing symptoms in a child with impaired communication; the number of subspecialists managing various problems with overlap; and the inability to test when the CNS is the cause of the intractable problem. All of this can increase the likelihood of invasive testing and interventions with limited benefit.

Areas that deserve attention, whether from a PPC team or the clinical care providers of such children, include: relief of suffering experienced by families as a result of social isolation and the stress associated with providing complex home-based care for ones child; guilt related to the pregnancy, the child's genetic diagnosis, or to a CNS injury; and the spiritual distress of 'why has this happened.' The American Academy of Pediatrics endorses the use of PPC for advanced symptom treatment, complicated decision-making that involves uncertainty, and for social and spiritual needs beyond what the primary care team can provide [1▪▪].

Uncertainty is a common theme in PPC, including children with neurological impairment. There is a wide range of outcomes, even within the same diagnosis. This starts with the perinatal identification of life-limiting conditions, with families needing to prepare for a range of outcomes. One programme's 5-year review of perinatal referrals, most with genetic or neurostructural conditions considered potentially lethal, identified 29% of live-born births surviving for more than 72 h, some for more than 1 month [16▪▪]. A review of survival of children with hydranencephaly found a steeper mortality in the first 2 years and a more gradual decline for those who survived beyond the first 2 years [17]. Other conditions with this pattern include alobar holoprosencephaly (HPE), the most severe form of HPE, along with trisomy 13 and 18. Although many deaths occur within the first days to weeks of life, those infants who survive the first month are likely to survive beyond infancy. Medical teams may prepare a family for a child's death, including following a decision to discontinue life-prolonging interventions. Parents can face the distress of preparing for this outcome and then seeing their child survive [18]. Indicating certainty of outcome when that outcome does not occur can result in distress for a family and lead to mistrust.

PPC can lessen the distress that is inherent with these challenges. Following a palliative care consult, a higher percentage of families of children with neuromuscular disorders and severe cognitive impairment elected to forgo life sustaining treatment (LST) interventions compared with children with other diagnoses. The most frequent goals of care identified for all children in this study included comfort/avoidance of suffering and improving or maintaining health [5]. The decisions to forgo LST following a PPC consult suggests both the under-recognition of suffering and the challenge encountered by medical teams of discussing the diminishing ability to maintain health or lessen decline. A retrospective review of hospital resource utilization identified a significant reduction in hospital length of stay following provision of PPC for the noncancer patients, with neurologic and genetic conditions accounting for a majority of this group [19▪▪]. This is consistent with literature indicating that earlier conversations result in shorter hospital stays and fewer aggressive interventions at the end of life. PPC teams may have less knowledge about the specifics of many of the rare disorders that alter function of the CNS, yet they have a framework to navigate these challenges.

PPC teams can also assist with the challenges that arise as home care plans shift from disease-modifying therapy, often provided by home care nurses for years, to care plans that promote comfort and lessen prolonged suffering [20]. This can include support for the home care team, given the strong relationships that often develop [15,20]. Other challenges that deserve expert support include complex care coordination and complexities with insurance [20].

It can be difficult for medical teams to set aside the traditional medical model of prognosis and predicting when the disease trajectory will become end of life as the framework for decision-making. Prognostic uncertainty is not unique to children with neurological impairment. What is unique is the lack of biomarkers that define when interventions are beneficial, when treatment is no longer curative, or there is further disease progression, such as pulmonary function tests for children with cystic fibrosis or Duchenne muscular dystrophy, or blood counts and tumor burden in children with cancer. Decision-making for families of children with neurological impairment is often the path of least regret. Fortunately, PPC can assist with improving the certainty of a family's decision. Given prognostic uncertainty, goals of care are an essential guide to decision-making when the outcome is uncertain, and yet they often remain poorly defined [5].

Some goals of care are common for all life-threatening conditions, such as to maintain comfort and promote health. Other goals, such as the preferred location of death, have been predominantly studied in children with cancer. When parents have the opportunity to consider the preferred location of death for their child, children with cancer were more likely to die at home [21]. Parents who had the opportunity to plan were also less likely to have preferred a different location of death. Other families may benefit from flexibility, including the need to move back and forth between settings. There is limited information about planning location of death for children with neurological impairment and how this may factor into decision-making [21].

Though comfort is often the most common goal identified, symptom identification and treatment remains challenging in nonverbal children with neurological impairment [22]. Symptoms identified in children with neurological impairment included pain, agitation, impaired sleep, muscle spasms, seizures, vomiting, constipation, breathing difficulties, and respiratory secretions [7,8▪]. Symptom management in children with neurological impairment is challenging and can be a source of distress for families given the unknown likelihood of improved comfort and the extent to which symptoms may signal disease progression and decline [7,8▪]. Symptom treatment includes medications and nonpharmacologic interventions, such as a vibrating mat

Table 1. Areas for consideration as a result of severe CNS impairment

Hoping/benefit	Preparing/harm
Risk of life-threatening events	
Risks that may be identified: impaired respiratory function, disordered central breathing with transient episodes of apnea	''You indicated that you want interventions if the illness is reversible. If this is not possible to know, what would be important to you?''
Identifying the risk of a life-threatening respiratory illness occurring in the next 12 months does not mean that event will occur	Information indicating risk of life-threatening event with first illness: no cough, no gag reflex, severe hypotonia, disordered central breathing with prolonged pauses; with future events: increasing use of chronic interventions to maintain respiratory health, increasing frequency of respiratory illnesses and hospitalizations, declining recovery following acute treatment, declining baseline respiratory health
''This is an opportunity for us to understand what is important to you without an expectation for any specific decision''	
''We continue to hope with you for benefit from the interventions added to the medical care plan that you have so carefully considered''	
Risk of persistent, intractable physical suffering (irritability, pain, muscle spasms)	
Persistent pain behaviors and muscle spasms often improve following the use of two or three drugs with different mechanisms of action: gabapentinoids, TCA, clonidine, opioids including methadone [22,23▪▪]	''I know that comfort is an important goal. I worry that it has been difficult to meet this goal or that it will only be possible with increased sedation. What are your thoughts?''
Persistent symptoms may be because of: loss of inhibitory control of the CNS; involvement of the spinothalamic tract (central neuropathic pain) resulting in a lower threshold to symptom generation, including pain related to normal distention of the gastrointestinal tract and bladder; impairment of the central autonomic nervous system with problems including pain and gastrointestinal symptoms; muscle spasms secondary to other pain sources	In addition to nociceptive pain sources, the CNS can be the source of symptoms
	Potential CNS sources cannot be 'fixed' or eliminated. Medications can decrease symptoms by increasing inhibition or decreasing excitation in the CNS. Many children will have a decrease in symptoms with drug trials, some will not have the degree of benefit desired, and symptoms originating from the CNS can return or persist.
Risk of intractable gastrointestinal symptoms (vomiting, retching, pain)	
Persistent vomiting, retching, and pain localized to the gastrointestinal tract may improve following the use of several interventions: proton pump inhibitor, gabapentinoid, cyproheptadine, tricyclic antidepressant, jejunostomy-tube [23▪▪]	''I know that comfort is an important goal. I worry that it has become more difficult to improve the gastrointestinal symptoms. What are your worries and thoughts?''
Sources of symptoms can include CNS impairment of the thalamus and the autonomic nervous system	Some children will benefit from a care plan that focuses on feeding to comfort rather than to a 'required' amount
Risk of irreversible decline in the CNS	
Potential features: increased frequency of low body temperature, low heart rate, and amount of sleep; intermittent self-resolving episodes of apnea; slowing of intestinal motility; hands and feet that are intermittently mottled or blue; increasing vomiting and pain localized to the gastrointestinal tract; increasing agitation, muscle spasms, arching, and stiffening, despite multiple medication trials	''What is important to you as we consider what these new features may be telling us about your son?''
These new features can occur transiently in some children over many months to years	These problems can occur intermittently in children with neurological impairment. Progressive, irreversible decline is often distinguished by an increasing number of problems that are controlled by the CNS and the frequency of the episodes. When such changes are noted, it is beneficial to consider 'reversible' sources of problems, such as medication toxicity, while simultaneously being mindful that this may be part of a progressive, irreversible decline in CNS function.

Table 1 (*Continued*)

Hoping/benefit	Preparing/harm
''Identifying these features does not mean that decline will continue, rather it alerts us to the possibility''	
Surgical interventions with unknown benefit (Nissen fundoplication, scoliosis surgery, tracheostomy, tracheal separation)	
Greater benefit when the surgical intervention addresses the single source of the problem versus only one of several contributing problems	''What is most important to you as you consider the information provided by the medical team and surgeon?''
Example: tracheotomy for anatomical airway obstruction with no other contributing problems versus a child with neurological impairment and multiple problems (impaired mucus mobilization, hypoventilation, aspiration, scoliosis)	Less benefit yet the same risk from these interventions when multiple problems contribute to compromised respiratory health
	Greater risk in children with declining health over time
CPR, intubation and time-limited trial of mechanical ventilation	
May prevent immediate death	''What is most important to you as you consider this information?''
May lengthen life by a year or more	Risk of rib fractures from chest compressions because of osteoporosis
Retrospective review of 22 children with severe neurological impairment intubated for respiratory failure: 50% were alive at 1 year (39% of those indicated to have 'chronic pulmonary problems'); six (27%) of the children alive at 1 year had no reintubation in the ICU and no further hospitalizations [26]	Risk of further brain injury because of hypoxia
	Parent unable to hold child at the end of life
	Child may not be able to come off the ventilator
	Underlying respiratory problems will be no better than before and potentially worse
Noninvasive treatment plans	
The last stage of life is not medically defined	May shorten life
Care at the end of life does not involve discomfort from tubes, tests, and procedures	May feel like ''giving up''
	Requires a skilled team available 24/7 to support such a care plan in the home

CNS, central nervous system; CPR, cardiopulmonary resuscitation; TCA, tricyclic antidepressant.

when a child with neurological impairment has persistent pain behaviors, as well as discontinuing interventions that are prolonging suffering [22,23▪▪]. For children with neurological impairment, this can include the decision to forgo medical nutrition by feeding tube or to feed to comfort, when tube feedings are the source of or are prolonging significant discomfort and suffering [24▪▪,25]. In this case series, discontinuing medical nutrition and hydration was considered by parents to be an acceptable decision and to contribute to a death that was peaceful and comfortable [24▪▪].

PPC teams also serve a role in the education of all general and subspecialty pediatricians [1▪▪]. This is in keeping with the goal of developing general competencies for all in such areas as basic pain and symptom management as well as advance care discussions, and the recognition of when to obtain specialized PPC consultation [1▪▪]. The details summarized earlier can help when considering the 'when' of obtaining a consult earlier in the disease course. First, it helps to remember that PPC does not lessen hope or increase distress. Second, PPC increases the likelihood that invasive interventions will not be used at the end of life and will occur at a preferred location. Yet how should we approach the idea that PPC is best considered implemented at the time of diagnosis in children with neurological impairment?

In children with neurological impairment, it is essential to start with the premise that it is challenging to know when a life-threatening event will occur or what the level of recovery will be when events do occur. Timing of PPC is ideally occurring because of the potential for a problem such as persistent suffering or the risk for a future life-threatening event, not dependent on knowing with certainty that these will happen. This is consistent with the duality that families are already living with as they celebrate small victories and worry about the future.

Discussions with families can acknowledge when information suggests that a life-threatening event may happen in the next year, the risk of ongoing decline with maximal disease-modifying care, or the increasing difficulty of improving comfort, while hoping and acknowledging the inability to know that these outcomes will occur. Ideally, recognizing earlier points in time to introduce palliative care can improve our ability to allow discussions during times of stability rather than only at times of crisis.

Table 1 intends to highlight such specific considerations. It utilizes the framework of 'hope' and 'prepare'. As an example, experience suggests that many children with neurological impairment will have a decrease in pain features after one or two medication trials, yet some will have symptoms that remain more difficult to control. Just as epilepsy can become more difficult to control after two or three failed medications, symptoms may remain more intractable in some. Such a circumstance deserves expertise in symptom management along with a comprehensive review of how the child's care plan is meeting the identified goals of care.

CONCLUSION

The information in Table 1 is best viewed as identifying opportunities to explicitly define goals of care, how such goals guide advance care planning, and when palliative care consults can be considered. It is intended as a framework of using goals of care as an essential guide to decision-making as families navigate hope and uncertainty. Earlier integration of PPC allows families to be better informed about options and supported throughout their child's life. For children with neurological impairment, this is essential given the shift that can occur gradually over months to years, increasing the challenge of recognizing when the benefit of interventions is diminishing or is resulting in increased suffering.

There is clear benefit to the provision of PPC for the children with metabolic and neurological diseases, along with their families. There are also many areas for future study. These include how the families of such children approach decision-making and how the integration of PPC influences bereavement. Specific considerations include how to identify and treat distressing symptoms and when persistent symptoms are likely to remain intractable. And of course overriding all of this are the spiritual, racial, ethnic, and socioeconomic factors that influence decision-making, as well as the range of options influenced by the availability of pediatric home care support through PPC and hospice teams. It is never too early to allow the integration of PPC, as our knowledge of the role of PPC for this group of children continues to evolve. This recognition will help minimize the lost opportunity to assist parents as they navigate the complexity of care needs for their child and family.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
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